Development of the conjugate addition/Nitro-Mannich reaction

A Thesis presented by

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In Part Fulfilment of the requirement for

the degree of Doctor of Philosophy

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January 2013

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I, Andreas Kalogirou confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Date……

Abstract

This thesis describes the development of the conjugate addition/nitro-Mannich reaction and its use in the synthesis of useful molecules like pyrrolidin-2-ones and piperazin-2-ones. The introductory chapter of this thesis outlines the literature related to the nitro-Mannich reaction, describing the different existing methodologies for performing the reaction in diastereo- and enantioselective manner. The synthetic applications of the reaction are also described, especially its uses in the synthesis of biologically active natural products. Moreover, the syntheses and uses of two classes of compounds, pyrrolidin-2-ones and piperazin-2-ones are briefly discussed.

The results and discussion chapter starts by presenting the use of a one-pot conjugate addition/nitro-Mannich/lactamisation reaction in the synthesis of densely functionalised pyrrolidin-2-ones. The development of an asymmetric protocol, as well as some functionalisations of the pyrrolidinone core are also described. Our efforts to synthesise human neutrophil elastase inhibitor GW311616A using the developed methodology are then detailed.

The next part of the results and discussion chapter portrays the development of a conjugate addition/nitro-Mannich reaction of non-zinc nucleophiles to ethyl 3-nitroacrylate and *β*-nitrostyrene. The scope and limitations of the reaction were investigated using a variety of different nucleophiles including amines, thiols, phosphines, alcohols, enolates and nitriles.

Finally, our work towards synthesising the biologically active piperazin-2-one *piperazirum*, using the nitro-Mannich methodology is described. The diastereoselective synthesis and characterisation of a densely functionalised piperazin-2-one was accomplished.

A detailed description of the experimental details and analytical data for all novel compounds is described in the experimental section. Tables of coupling constants and X-ray crystallographic data are presented in the appendices section, followed by a list of literature references.

Acknowledgements

First of all I would like to thank my supervisor, Prof. Jim Anderson for giving me the opportunity to work in this very interesting subject and for his constant guidance and constructive criticism. I thank him for giving me valuable knowledge in chemistry during our weekly group meetings and our discussions.

I would like to thank UCL's technical staff for their help, especially Dr Abil Aliev and Dr Lisa Harrys. I would also like to thank Dr Graham J. Tizzard at the National Crystallography Service in Southampton for obtaining the X-ray crystal structures presented in this thesis. I would also like to thank Prof. Willie Motherwell for his inspiring discussions.

Moreover, I am grateful to all the past and present members of the Anderson group for their help and support. I would like to give special thanks to György, Rafa, Helen, Paul and Emily for their stimulating discussions and valuable suggestions that were important in developing this thesis.

A big thanks goes to my parents for their financial support, without which this thesis would not be possible, as well as their constant encouragement and support. I also thank the "Cyprus State Scholarship Foundation" for their funding which was also important for my studies.

I would like to thank my sister Anna for her help. Living in a foreign country is not easy and is made easier by having a member of the family nearby.

Finally I would like to thank my friends György and Aline for all their help and moral support. Without them life in London would not have been as colourful.

Abbreviations

ABCN	1,1'-Azobis(cyclohexanecarbonitrile)
Ac	Acetyl
AIBN	Azobisisobutyronitrile
atm	Atmospheres
B	Base
BINOL	1,1'-Bi(2-naphthol)
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOX	Bisoxazoline
Bu	Butyl
CAN	Ceric(IV) ammonium nitrate
Cbz	Carboxybenzyl
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
E	Electrophile
Et	Ethyl
equiv.	Equivalents

DIPEA	Diisopropylethylamine
DIBAL	Diisobutylaluminium hydride
EDC	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
h	Hours
Het	Heterocycle
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HPLC	High performance liquid chromatography
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
^{i}Bu	Isobutyl
^{i}Pr	Isopropyl
IR	Infrared
J	Coupling constant
LG	Leaving group
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
MOM	Methoxymethyl ether
MPTsOH II	polymer-bound acid resin
MS	Molecular sieves
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
OMB	*ortho*-Methoxybenzyl

OMP	*ortho*-Methoxyphenyl
P	Protecting group
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
Pr	Propyl
*p*TSA	*para*-Toluenesulfonic acid
rt	Room temperature
sm	Starting material
S_N2	Bimolecular nucleophilic substitution
TBAF	Tetra-^{n}butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
^{t}Bu	*tert*-Butyl
Tf	Triflate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
Tol	*para*-Tolyl
LDA	Lithium diisopropylamide
Å	Angstrom
^{o}C	Degrees Centigrade

Table of Contents **Page**

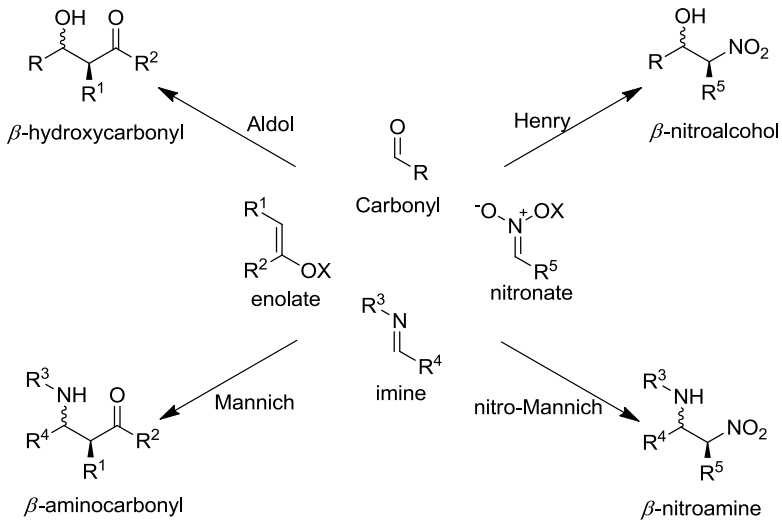
1. Introduction

One of the ongoing and fundamental challenges in organic chemistry is the synthesis of complex molecules. The installation of useful functional groups in a short and concise fashion is important in accessing such molecules in an efficient manner. There is a constant need for reactions that install a lot of functionality, in short steps and with high selectivity. The work carried out in this thesis in developing such processes will be described in the next chapter, whereas this chapter will focus on describing the current literature in four areas related to our work. Those are the development of the nitro-Mannich reaction, the conjugate addition of nucleophiles to nitroalkenes, the synthetic applications of the nitro-Mannich reaction and the synthesis and applications of piperazinones and pyrrolidinones.

1.1 The nitro-Mannich reaction

1.1.1 Overview

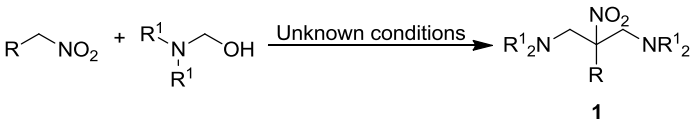
The nitro-Mannich (or aza-Henry) reaction is a member of the family of synthetically useful carbon-carbon bond forming reactions, specifically the ones where an active C-H nucleophile is added to a C=X bond (Scheme 1). The other three members of this group are the aldol, the nitro-aldol and the Mannich reaction. The aldol reaction, the most thoroughly explored of the group, involves nucleophilic addition of an enolate to a carbonyl electrophile.[1] Replacing the enolate nucleophile with a nitronate gives the nitro-Aldol (Henry) reaction,[2] while replacing the carbonyl electrophile with an imine gives the Mannich reaction,[3] both of which have been extensively researched. The last member of the family and the least explored one is the nitro-Mannich reaction, where a nitronate nucleophile adds to an imine electrophile. A brief review of the work in this field follows.



Scheme 1. Addition of active C-H nucleophiles to C=X electrophiles

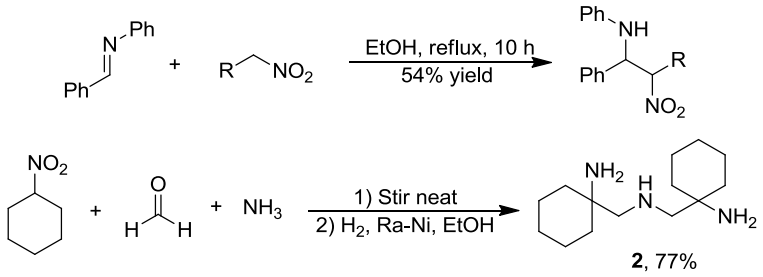
1.1.2 Initial development

Louis Henry first reported the nitro-Mannich reaction in 1896[4] after first reporting the Henry reaction the previous year.[5] Henry discovered that nitroalkanes could add to hemiaminals to form *β*-nitroamines (Scheme 2), however the exact conditions he used were not described. Presumably the hemiaminal loses a molecule of water to form an iminium ion, which is attacked by the nitronic acid tautomer of the nitroalkane. The process is repeated to give product **1**.



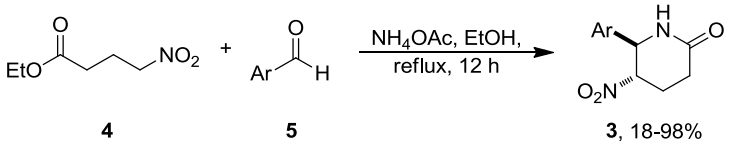
Scheme 2. First reported nitro-Mannich reaction

A very limited number of publications on the nitro-Mannich reaction appeared over the next hundred years, most of them in the 1950s and those were of little scope and not stereoselective.[6,7] However, some development was made in the methodology of the reaction. For example, the imine was either added to the reaction mixture[8] or formed *in situ* by having an aldehyde and an amine as the reagents (Scheme 3).[9] Both of these methods are still used today.[10,11] It is noteworthy that Smiley was the first to use the nitro-Mannich reaction to make vicinal diamines **2** by reducing the product nitroamines.[9] The main use of the nitro-Mannich reaction today is for the synthesis of vicinal diamines.



Scheme 3. Early developments of the nitro-Mannich reaction

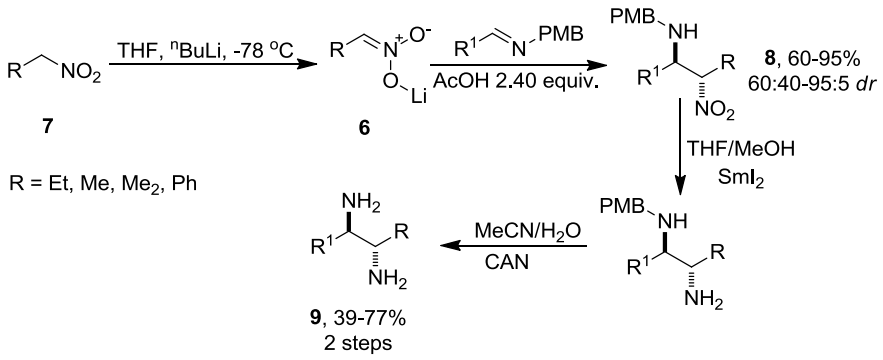
A few decades later (1976), Jain and co-workers reported the formation of piperidinones **3** by reaction of nitroester **4** with aromatic aldehydes **5** and ammonium acetate (Scheme 4).[12] The reaction gave piperidinones **3** in variable yields, as the *anti* diastereoisomers, but was only efficient using ammonia and not for other amines.



Scheme 4. Synthesis of piperidinones *via* nitro-Mannich reaction

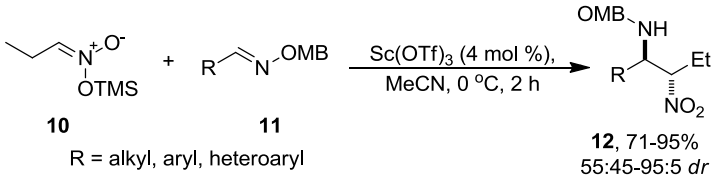
1.1.3 Non-catalytic nitro-Mannich reactions

The first diastereoselective nitro-Mannich reaction was reported by the Anderson group in 1998 (Scheme 5).[13] Anderson and co-workers reported the 1,4-addition of nitronate ions **6**, produced *in situ* from treatment of nitroalkanes **7** with ^{n}BuLi, on *N*-PMB protected imines in the presence of a Brønsted acid, to yield *anti*-rich *β*-nitroamines **8** in excellent yields and diastereoselectivity. The products **8** were also subsequently reduced with SmI_2 and the PMB group cleaved on treatment with CAN to give vicinal diamines **9** (Scheme 5).



Scheme 5. The first diastereoselective nitro-Mannich reaction

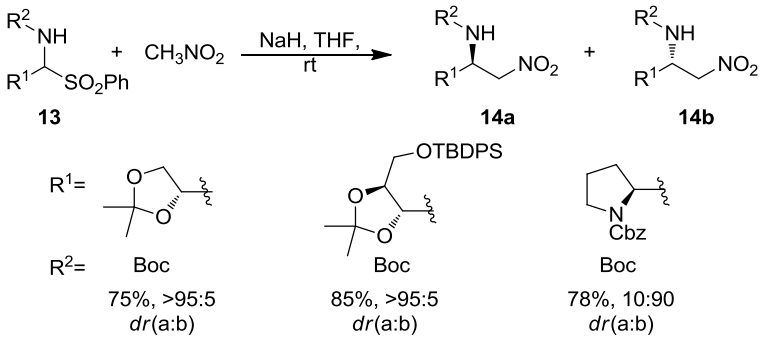
Seven years later, the Anderson group showed that a silyl protected nitronate could also be used to perform the reaction instead of the free anion.[14] Lewis acids were used to promote the addition of trimethylsilyl nitropropanate **10** to imines **11** to give *β*-nitroamines **12** (Scheme 6). Several Lewis acids were investigated, such as $BF_3{\cdot}Et_2O$, $TiCl_2(O^iPr)_2$ and lanthanide triflates and the best results were obtained using $Sc(OTf)_3$. Interestingly it was found that use of OMB (*ortho*-methoxybenzyl) instead of PMP (*para*-methoxyphenyl) and PMB (*para*-methoxybenzyl) protected imines greatly improved the yields and *anti* selectivity of the reaction. The authors proved this to be both a steric and an electronic effect.[14]



Scheme 6. Nitro-Mannich reactions of silyl-nitronate **10**

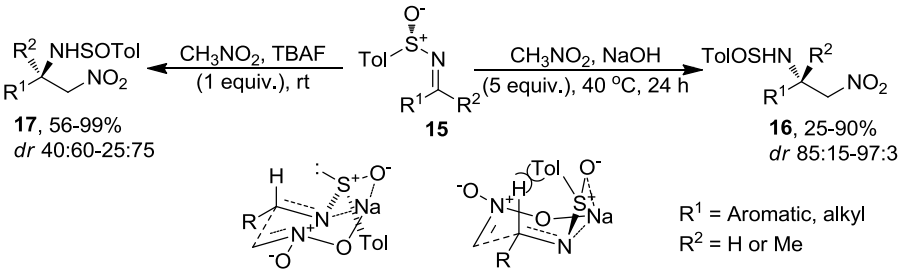
1.1.4 Non-catalytic enantioselective nitro-Mannich reactions

Only a small number of publications have reported examples of non-catalytic enantioselective nitro-Mannich reactions. These reactions required the presence of a chiral auxiliary in the imine, either on the imine nitrogen or on the part derived from the aldehyde. Petrini and co-workers reported the nitro-Mannich reaction of nitromethane with a variety of non-racemic chiral imines (Scheme 7).[15] The imines were generated *in situ* from amidosulfones **13** and gave medium-good yields of *β*-nitroamines **14a** and **14b** with good diastereoselectivity. Although limited to nitromethane, this investigation showed that a nitro-Mannich reaction could be rendered stereoselective in the presence of a proximal chiral centre.



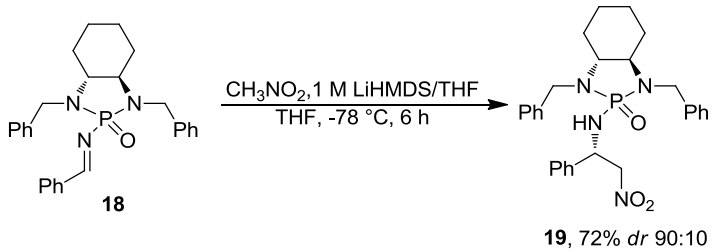
Scheme 7. Nitro-Mannich reaction in the presence of a chiral centre

The *N*-sulfinyl group, was successfully used by Garcia and co-workers as a chiral auxiliary. The authors reported the diastereoselective reaction of *N*-sulfinimines **15** with nitromethane and NaOH to yield enantiomerically pure *β*-nitroamines **16**. When TBAF was used as the base, the reaction was much faster and the diastereoselectivity inverted (Scheme 8).[16] The high selectivity with NaOH was explained by a cyclic transition state involving coordination of the sodium cation.



Scheme 8. A diastereoselective nitro-Mannich reaction with *N*-sulfinimines

Similarly, Li and co-workers described the asymmetric nitro-Mannich reaction with chiral *N*-phosphonoyl imines **18** (Scheme 9).[17] Even though only one example was reported, a good yield and enantioselectivity of product **19** was observed, while the chiral auxiliary could be later removed and recycled.

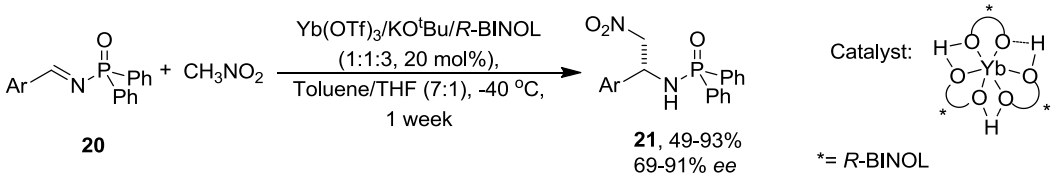


Scheme 9. Asymmetric nitro-Mannich reaction with chiral *N*-phosphonoyl imines

1.1.5 Metal-catalysed nitro-Mannich reactions

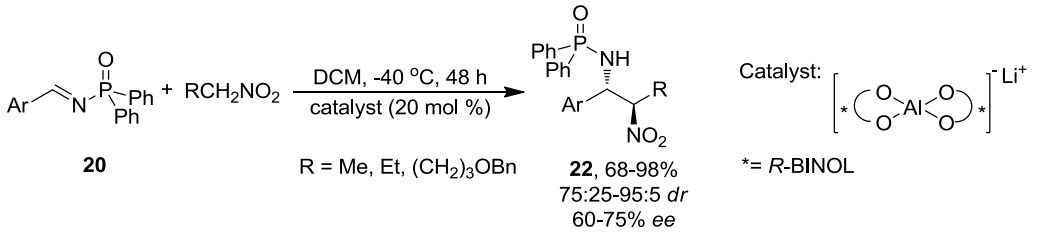
The first metal-catalysed enantioselective nitro-Mannich reaction was reported by Shibasaki and co-workers in 1999.[18] A Yb (III) complex, previously used in catalytic asymmetric Aldol reactions,[19] was used to catalyse the addition of nitromethane to *N*-phosphinoyl imines **20** to give products **21** which were isolated in good yields and enantioselectivities (Scheme 10). The reactive complex contained $Yb(O^iPr)_3$, KO^tBu and (*R*)-binapthol in a 1:1:3 ratio that formed the reactive mixed Lewis acid and Brønsted base catalyst. The authors argued that the phosphinoyl group on the imine was essential due to coordination to the metal centre. The reaction gave medium to

good yields and enantioselectivities, however was limited to nitromethane and aromatic imines and required 60 mol% of *R*-BINOL.



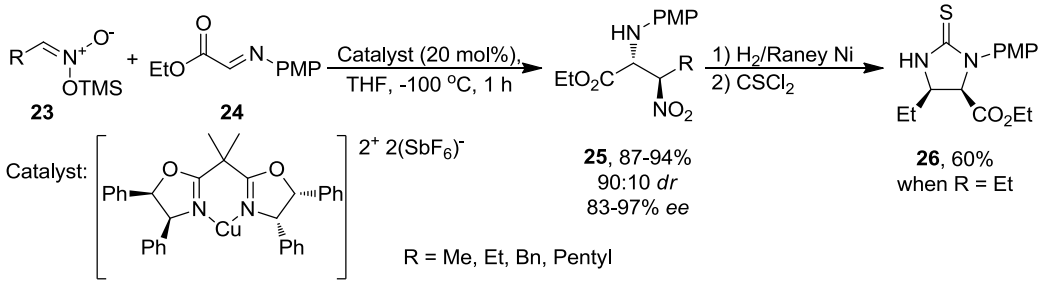
Scheme 10. The first metal-catalysed enantioselective nitro-Mannich reaction

A few years later, in 2001, the same authors reported an alternative procedure using an aluminium catalyst (Scheme 11).[20] The new catalyst was effective for a range of nitroalkanes and the reaction proceeded more rapidly, however the enantioselectivities of the products **22** were slightly lower.



Scheme 11. A metal-catalysed enantioselective nitro-Mannich reaction

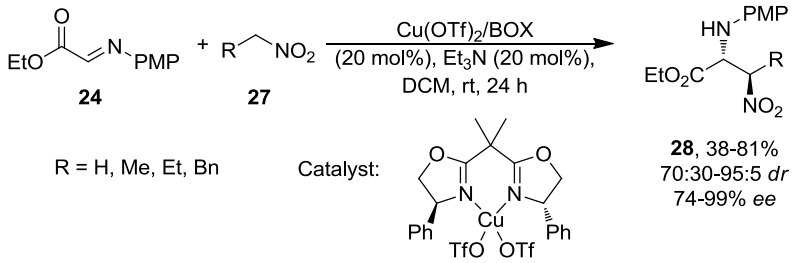
In the same year, Jørgensen and co-workers reported the enantioselective addition of silylnitronates **23** to PMP imine **24**, derived from ethyl glyoxylate, in the presence of a Cu(II)-BOX catalyst (Scheme 12).[21] The product *β*-nitroamines **25** were isolated in good yields and selectivities. The authors also reported the reduction of the ethyl analogue and subsequent reaction with thiophosgene to thioimidazolidinone **26**, which helped to deduce the absolute stereochemistry by X-ray crystallography.



Scheme 12. An enantioselective nitro-Mannich reaction with silylnitronates

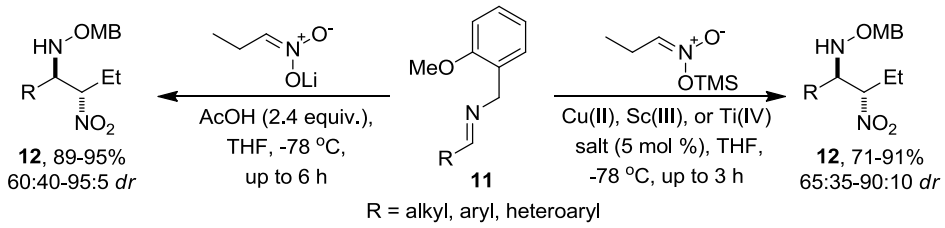
Shortly after this publication, the same group also reported the enantioselective addition of nitroalkanes **27** to the same imine **24** in the presence of a different Cu(II)-

BOX catalyst (Scheme 13).[22] The product *β*-nitro-*α*-amino esters **28** were obtained in good yields and excellent *dr* and *ee*, while the reactions were compatible with the presence of moisture and did not require the use of an inert atmosphere. However, this protocol only worked with glyoxylate imines as the ester oxygen and imine nitrogen provided a two-point binding site to the copper, which was essential in the catalysis mechanism.



Scheme 13. An enantioselective nitro-Mannich reaction catalysed by Cu(II)-BOX

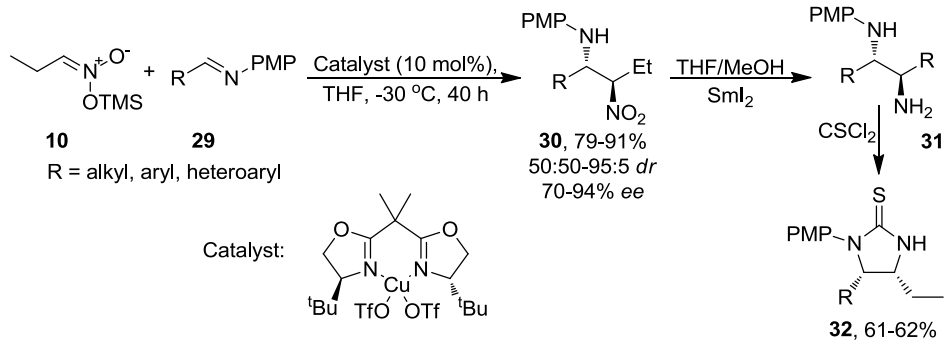
A few years later, in 2005, the Anderson group reported a diastereoselective nitro-Mannich reaction from OMB protected imines **11**. The reaction of **11** with either lithium nitropropanoate and acetic acid or trimethylsilyl nitropropanoate in the presence of a Lewis acid gave *anti*-rich *β*-nitroamines **12** in excellent yields and good diastereoselectivities (Scheme 14).[14] The authors argued that the OMB protecting group was better than other groups due to chelation with the Lewis acid.



Scheme 14. A Lewis and Brønsted acid catalysed nitro-Mannich reaction

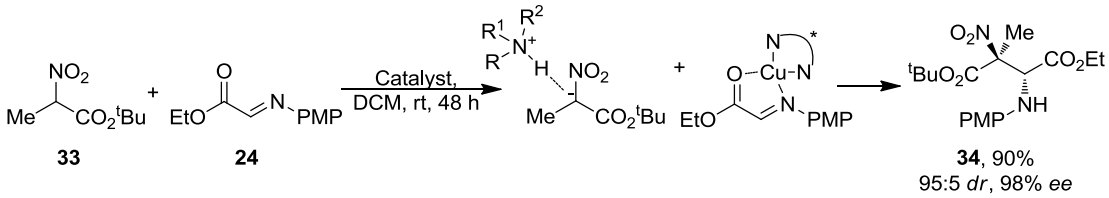
The Anderson group also reported a metal-catalysed enantioselective reaction[23] as a continuation of the work reported before with trimethylsilyl nitropropanate **10**.[14] This reaction also used a ^{t}Bu-BOX-Cu(II) catalyst with small loadings. The reaction worked well for a variety of alkyl, aryl and heterocyclic *N*-PMP imines **29** and gave good diastereo- and enantioselectivities and yields of products **30** (Scheme 15). In contrast to the previous work, the authors reported that PMP protected imines gave better enantioselectivities than OMB protected ones. This was attributed to the higher reactivity of the OMB imines, which gave a significant racemic background reaction.

The products **30** were reduced to diamines **31** with SmI_2 and then reacted with thiophosgene to give the corresponding thioimidazolidinones **32**. In the same way as before, the presence of the heavy sulfur atom allowed for the assignment of the absolute stereochemistry of the products using X-ray crystallography.



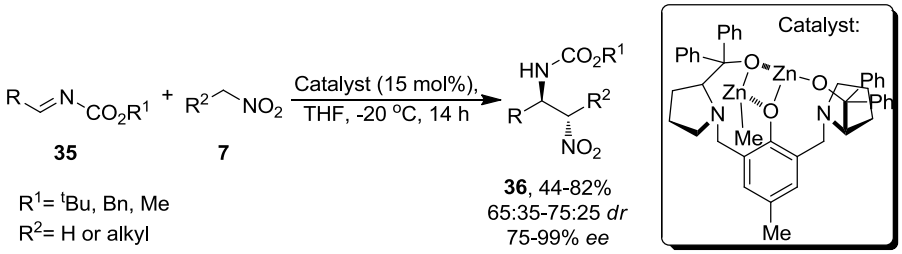
Scheme 15. An enantioselective nitro-Mannich reaction catalysed by Cu(II)-BOX

In the same year, Jørgensen and co-workers reported an update of their methodology, using a cinchona alkaloid and a Ph-BOX-Cu(II) catalyst to affect a chiral nitro-Mannich reaction with secondary nitroalkane **33** and imine **24** (Scheme 16).[24] The authors proposed that the cinchona catalyst was needed to deprotonate the nitroalkane and the Lewis acid to activate the imine, thereby forming a diastereomerically matched pair (Scheme 16). The reaction required a low catalyst loading and the product *β*-nitroamine **34**, which contains two vicinal stereocentres, was isolated in good yield and excellent enantioselectivity.



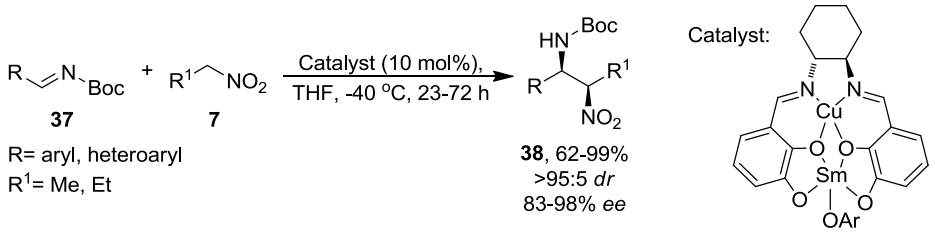
Scheme 16. An enantioselective nitro-Mannich reaction by a dual activation catalyst

In 2007 Trost and co-workers used a binuclear zinc catalyst to give an asymmetric nitro-Mannich reaction between carbamate protected imines **35** and nitroalkanes **7** (Scheme 17).[25] The reaction worked well with aryl, alkyl and even *α*,*β*-unsaturated imines to afford the desired products **36** in good yield and *ee*.



Scheme 17. An enantioselective nitro-Mannich reaction by binuclear zinc catalyst

In the same year Shibasaki and co-workers reported the first asymmetric *syn*-selective nitro-Mannich reaction of *N*-Boc protected imines **37** with nitroalkanes **7**, using a heterobimetallic catalyst complex comprised of a dinucleating Schiff base ligand and both Cu^{2+} and Sm^{3+} ions as well as a phenoxide ion (Scheme 18).[26] The yields and stereoselectivities of products **38** were excellent, however the reaction did not proceed well with *ortho*-substituted aryl imines. The authors argued that the catalyst works by coordination of the nitro group to the samarium centre and the imine (*via* the Boc carbonyl) to the copper centre.



Scheme 18. The first asymmetric *syn*-selective nitro-Mannich reaction

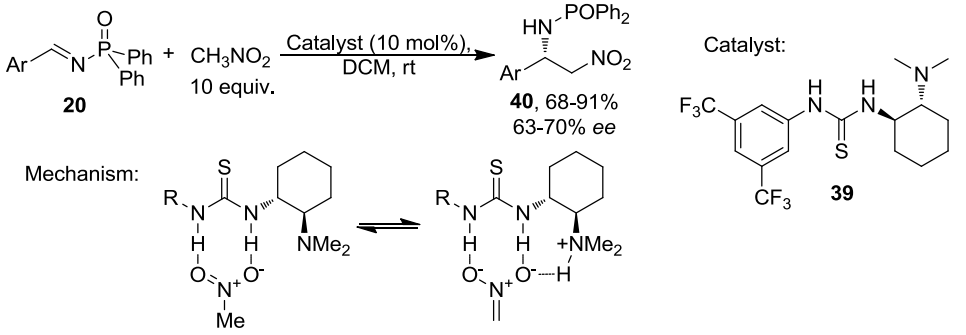
More metal-catalysed nitro-Mannich reactions have been reported, however those follow similar protocols to the ones presented above. The next section will focus on the development of various organocatalytic protocols.

1.1.6 Organocatalytic nitro-Mannich reactions

Organocatalysis has been increasingly used in asymmetric synthesis,[27] as it has some advantages over heavy metal catalysis. Organocatalysts tend to be cheaper, less toxic and more tolerant to air and moisture than metallic catalysts, while they often achieve high enantio- and diastereoselectivities. However, they do tend to require high loadings and long reaction times.

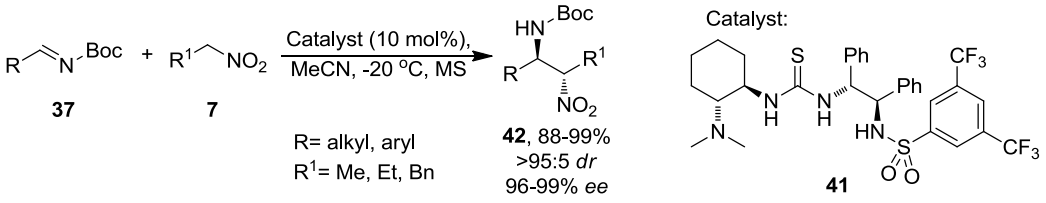
The first organocatalytic nitro-Mannich reaction appeared in 2004 by Takemoto and co-workers (Scheme 19).[28] The authors reported that thiourea organocatalyst **39** affected the coupling of nitromethane with a range of *N*-phosphinoyl protected aryl

imines **20**. The authors based their work on previous studies on the Michael addition of malonates to nitro olefins.[29] They suggested that the thiourea moiety in the catalyst hydrogen-bonds to the nitro group of the nitroalkane, facilitating its deprotonation by the neighbouring tertiary amino group (Scheme 19). The reaction gave good yields but only moderate enantioselectivities of products **40** and was limited mainly to nitromethane and to aromatic imines.



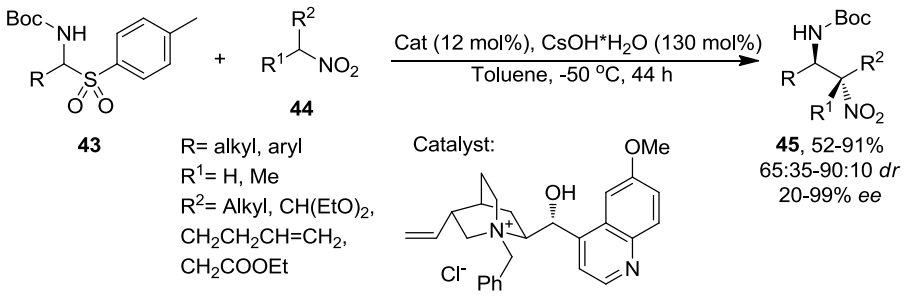
Scheme 19. The first organocatalytic nitro-Mannich reaction

Many other reports of thiourea-catalysed nitro-Mannich procedures appeared after Takemoto's original report. The most impressive results were published by Wang and co-workers (Scheme 20).[30] Thiourea catalyst **41** with two diamine units was used and the product *β*-nitroamines **42** were isolated in excellent yield and stereoselectivity.



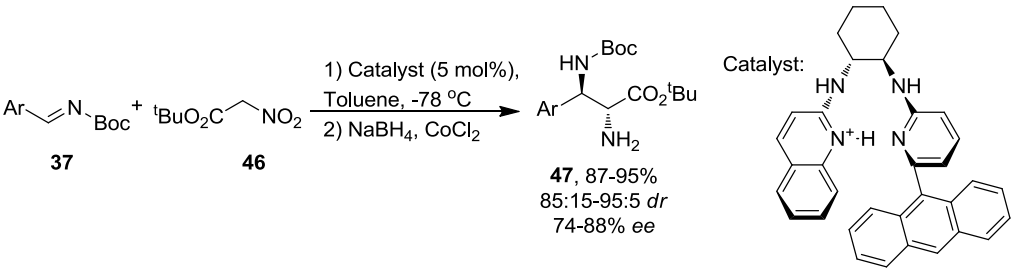
Scheme 20. Wang's thiourea-catalysed nitro-Mannich

Cinchona alkaloids have been used as organocatalysts in the nitro-Mannich reaction. An interesting report by Palomo and co-workers used a quinine alkaloid as a chiral phase transfer catalyst to perform the reaction between *N*-Boc protected imines and nitroalkanes (Scheme 21).[31] The imines were formed *in situ* from elimination of *α*-amido sulfones **43** under basic reaction conditions. The reaction was shown to tolerate a range of nitroalkanes **44** and enolisable imines, although lower yields and enantioselectivities were observed for secondary nitroalkanes. The product *β*-nitroamines **45** were converted into vicinal diamines, *β*-amino acids and allylic amines.



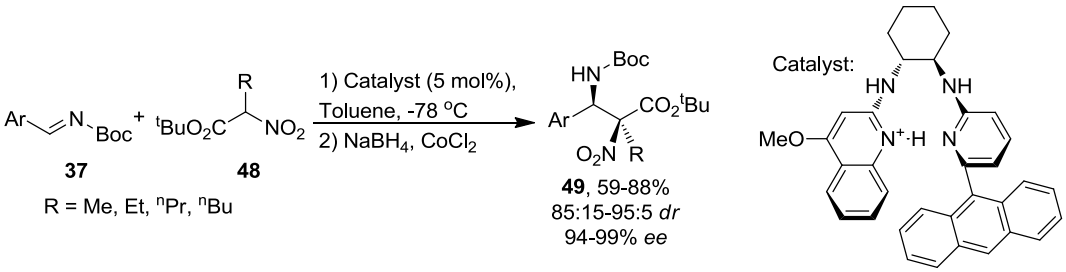
Scheme 21. A Cinchona alkaloid organocatalysed nitro-Mannich reaction

One other organocatalytic strategy used in the nitro-Mannich reaction is chiral proton catalysis, first reported by Johnston and co-workers in 2007.[32] This report described the addition of nitroesters **46** to *N*-Boc protected imines **37** using an asymmetric bis(amidine) catalyst to give, after reduction, vicinal diamines **47** in good yields and selectivities (Scheme 22).



Scheme 22. A stereoselective nitro-Mannich reaction by chiral proton catalysis

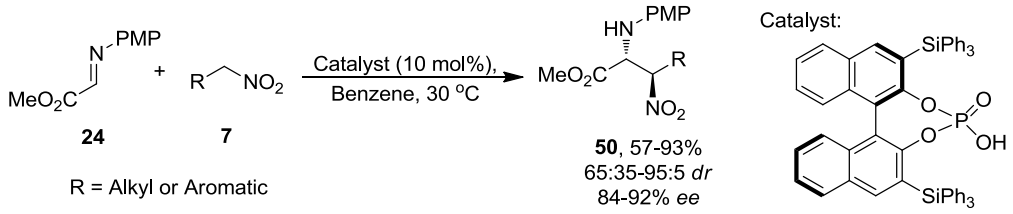
Soon after the previous report, the same group reported an expansion of their methodology using a similar catalyst with secondary nitroalkanes **48** (Scheme 23).[33] The new methodology gave *syn*-*α*-amino-*β*-nitro esters **49** in slightly lower yields but excellent enantioselectivity.



Scheme 23. The stereoselective synthesis of *syn*-*α*-amino-*β*-nitro esters **49**

An alternative chiral proton catalyst was reported by Rueping and Antonchick.[34] Reaction of *α*-imino ester **24** with various primary nitroalkanes **7** in the presence of a

phosphoric acid catalyst, gave *β*-nitroamines **50** in good yields and enantioselectivity but variable diastereoselectivities (Scheme 24).



Scheme 24. A Brønsted acid catalysed nitro-Mannich reaction

All the above-mentioned nitro-Mannich protocols have one common feature which is the origin of the nitronate anion. In most cases this anion originated from nitroalkanes or their derivatives (silyl nitronates). However, a limited number of nitroalkanes are commercially available or can be synthesised easily. A solution to this problem was provided by the use of nitroalkenes and formation of the reactive nitronate species by the conjugate addition of a suitable nucleophile, followed by a nitro-Mannich reaction in a tandem fashion. The use of nitroalkenes increases the variability and scope of the nitro-Mannich reaction. The conjugate addition/nitro-Mannich reaction of nitroalkenes with dialkylzincs and Superhydride® was investigated recently by the Anderson group and will be described in section 2.1.[35,36,37] The literature of the conjugate additions to nitroalkenes will be reviewed in the following section.

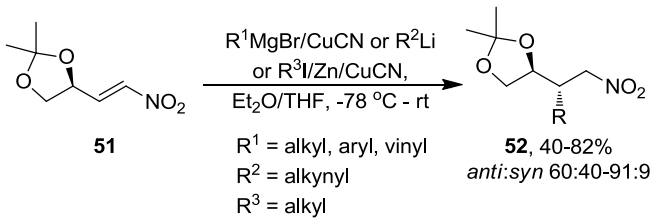
1.2 Stereoselective 1,4-addition to nitroalkenes

Nitroalkenes are one of the most useful groups of synthetic building blocks.[38] The presence of the highly electron withdrawing nitro group, controls their chemistry, making these olefins highly susceptible to 1,4-conjugate addition of nucleophiles, enabling the synthesis of more complex molecules.[39] A range of nucleophiles could perform a conjugate addition on a nitroalkene in an enantioselective fashion including carbon, oxygen, nitrogen, sulfur and phosphorus nucleophiles.[39]

1.2.1 Substrate/auxiliary controlled 1,4-Additions

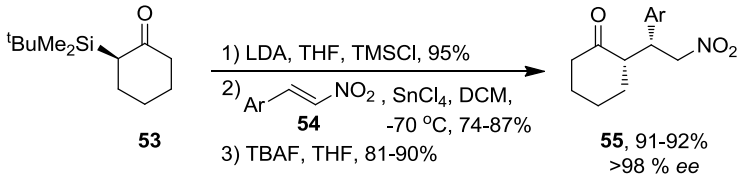
The stereoselective Michael additions of various carbon nucleophiles using a chiral substrate or auxiliary control is initially presented. A large number of such reactions have been reported, so a few representative examples will be given in this section.

In 1996, Pätzel and co-workers reported the 1,4-addition of organometallic reagents to nitro-olefins **51** derived from (*R*)-2,3-isopropylidene glyceraldehyde (Scheme 25).[40] The reactions gave mainly the *anti* adducts **52** in good diastereoselectivity.



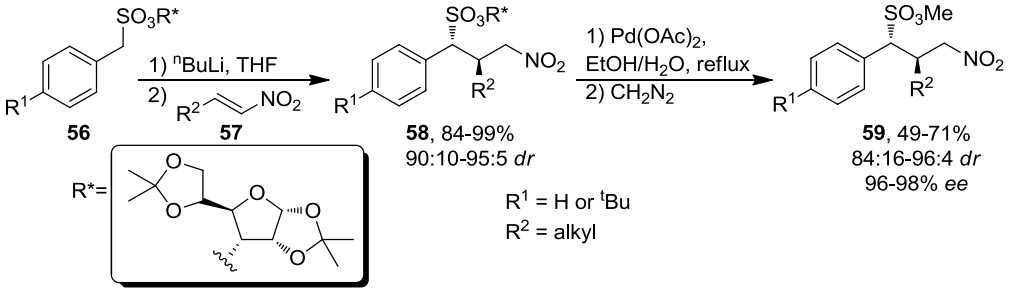
Scheme 25. A diastereoselective Michael addition to glyceraldehydes **51**

Enders and co-workers described the use of chiral α-silyl ketone **53** as a nucleophile in an enantioselective 1,4-addition reaction to nitroalkenes **54**, for the synthesis of α,β-disubstituted γ-nitro ketones **55**.[41] The ketone was first converted to a silyl enol ether and then reacted with the nitroalkene in the presence of $SnCl_4$ as the Lewis acid (Scheme 26). The silyl group was then removed with TBAF to give the products **55** in excellent diastereo- and enantioselectivities.



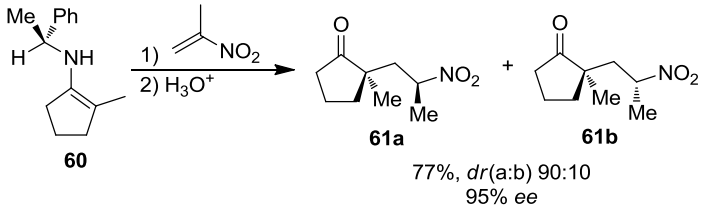
Scheme 26. A diastereoselective Michael addition to chiral α-silyl enol ethers

The same group also reported the use of a chiral sugar auxiliary to afford the diastereo- and enantioselective Michael addition of enantiopure sulfonates **56** on nitroalkenes **57** (Scheme 27).[42] The products **58** were isolated in high yields and selectivities and subsequently converted to sulfonates **59** and the absolute stereochemistry confirmed by X-ray crystallography.



Scheme 27. A diastereoselective Michael addition using a chiral sugar auxiliary

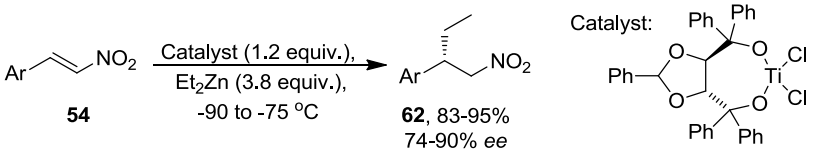
Another auxiliary-controlled conjugate addition reaction was reported by d'Angelo and co-workers.[43] Using chiral enamine **60** as the substrate, the 1,4-addition products **61a** and **61b** were isolated in good yields and selectivities (Scheme 28).



Scheme 28. Michael addition of a chiral enamine

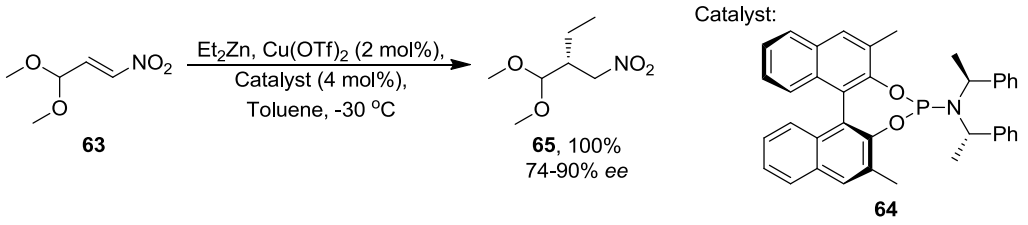
1.2.2 Metal-catalysed 1,4-Additions

Seebach and co-workers first reported the use of diethylzinc as a nucleophile in the conjugate addition to nitroalkenes, in the presence of Lewis acids such as $MgBr_2$, (Scheme 29).[44] They also showed that this conjugate addition to aromatic nitroalkenes **54** could become enantioselective when carried out in the presence of a chiral Ti-TADDOLate complex, to give the product nitroalkanes **62** in high yield and enantiomeric excess. The reaction was however not catalytic as 1.2 equivalents of the metal complex was required.



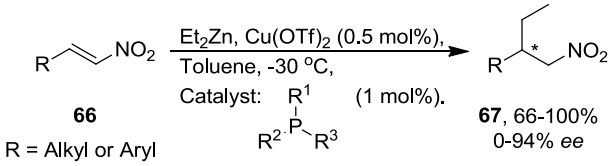
Scheme 29. The first metal-catalysed 1,4-addition

In 1998 Sewald and Wendisch developed an asymmetric catalytic conjugate addition of diethyl zinc to nitroalkene **63** using phosphoramidite ligand **64**, originally developed by Feringa (Scheme 30).[45,46]The product **65** was obtained in quantitative yield and high enantioselectivity.



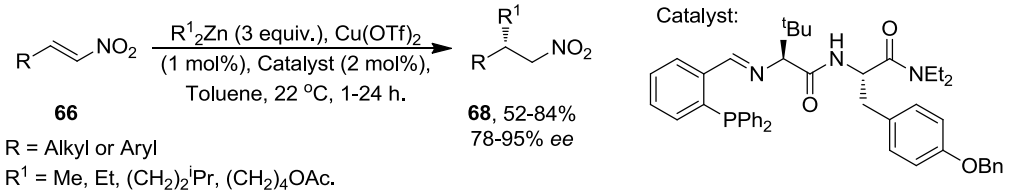
Scheme 30. A copper phosphoramidite catalysed 1,4-addition of Et_2Zn

Later, Wendisch's and Feringa's groups both expanded this methodology to asymmetric conjugate additions of dialkylzincs to nitroacrylates using the same chiral ligand.[47,48] The Alexakis group however, screened a whole range of phosphorus ligands and a variety of nitroalkenes **66** (Scheme 31).[49] The reaction required only small catalyst loadings, while both enantiomers could be accessed from different catalysts.



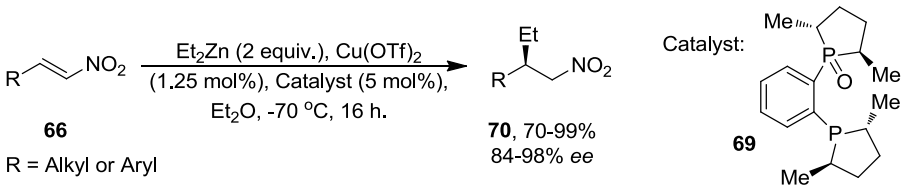
Scheme 31. A more general copper phosphoramidite catalysed Michael addition

Mampreian and Hoveyda reported the asymmetric Michael addition of dialkylzincs using a chiral dipeptide catalyst.[50] The catalyst was chosen after a screening of different dipeptides, that showed that both chiral centres were necessary. A few different dialkylzinc reagents were investigated (mainly Me_2Zn and Et_2Zn). In addition, a number of alkyl and aryl substituted nitroalkenes **66** and the 1,4-addition products **68** were isolated in good yields and selectivities (Scheme 32).



Scheme 32. An asymmetric 1,4-addition of dialkylzincs

Charette and co-workers demonstrated that Me-DuPHOS monoxide **69** was an effective ligand for copper in the asymmetric conjugate addition of diethylzinc on nitroalkenes (Scheme 33).[51] A screening of solvents showed that Et_2O and toluene gave the best yields and selectivities. The nitroalkane products **70** were isolated in good yields and *ee*. Moreover, it was possible to reduce the amount of copper and catalyst used to 1.25 and 2.50 mol % respectively, by adding an additive (20 mol %). The best additive was found to be pivalamide. The authors stated that the additive coordinates to the copper, thereby favouring a monomeric instead of a polymeric ethylcopper species which is more active.

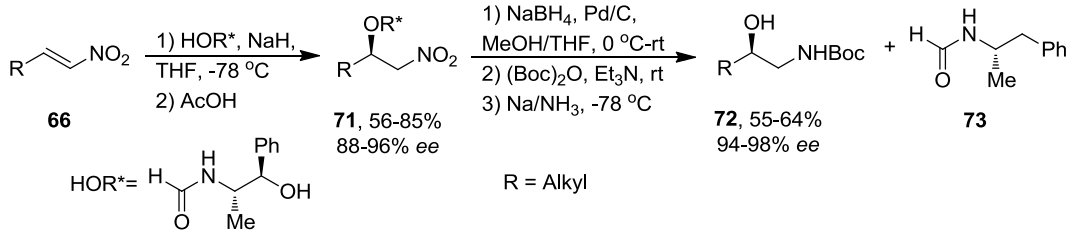


Scheme 33. Charette's asymmetric diethylzinc addition

1.2.3 1,4-Additions of Oxygen nucleophiles

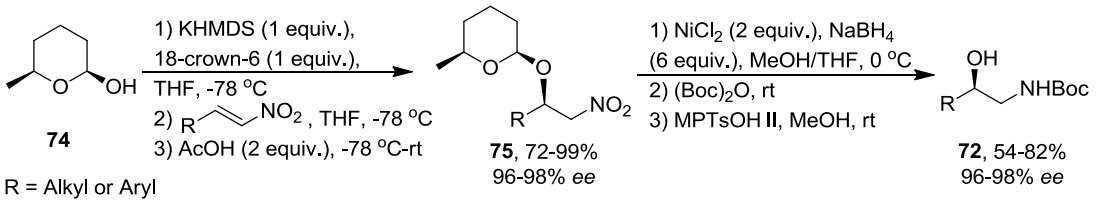
A large number of reports exist for the 1,4-addition of oxygen nucleophiles to nitroalkenes, however most of them were racemic.[52] This section concentrates on some synthetically useful asymmetric reactions.

Enders and co-workers reported the conjugate addition of (-)-*N*-formylnorephedrine to nitroalkenes **66** (Scheme 34).[53] This oxa-Michael reaction gave initially nitroethers **71**, which were then converted to vicinal amino alcohols **72** in good yields and excellent *ee*. The chiral auxiliary was removed in a Na/NH_3 reduction step and recovered as (*S*)-*N*-formylamphetamine **73**, while the absolute stereochemistry was confirmed by X-ray crystallography of **71**.



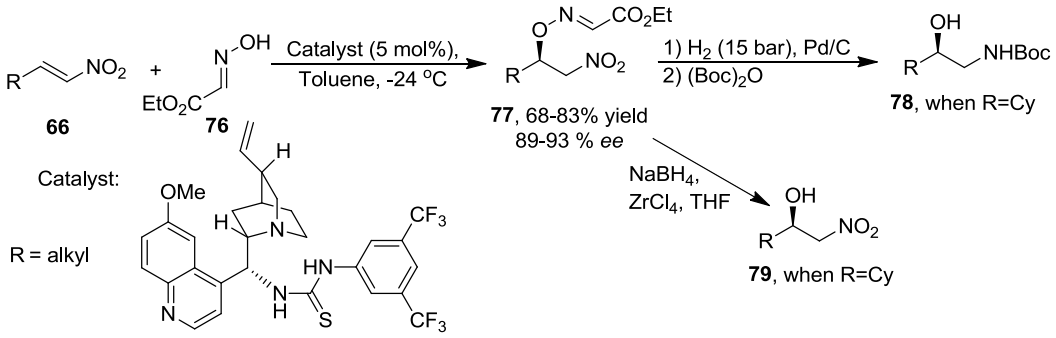
Scheme 34. Conjugate addition of (-)-*N*-formylnorephedrine

Later, in 2003, Dixon and co-workers reported the oxa-Michael conjugate addition of the "chiral water" reagent **74**.[54] Nitroalkanes **75** were formed in good yields and *ee* and were converted to enantioenriched aminoalcohols **72** after hydrolysis of the THP group (Scheme 35).



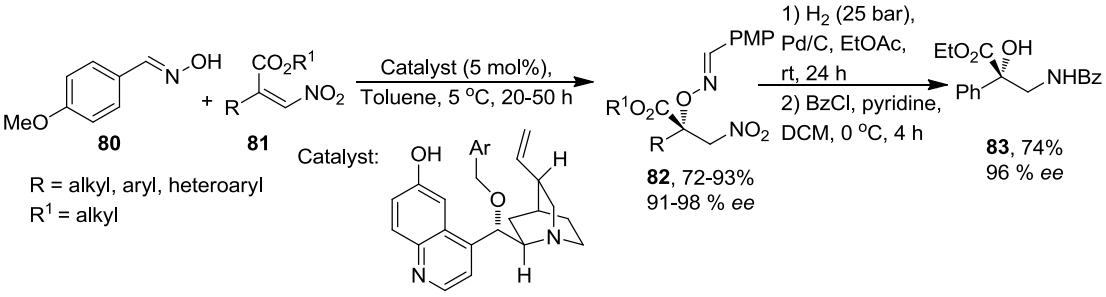
Scheme 35. The 1,4-addition of "chiral water" to nitroalkenes

An organocatalytic hydroxylation methodology was reported by Jørgensen and co-workers. The 1,4-addition of oxime **76** to nitroalkenes **66** catalysed by bifunctional thiourea-cinchona alkaloids, gave nitroalkanes **77** in good yields and *ee* (Scheme 36).[55] It was shown that products **77** could be easily converted to nitroalcohols **78** or nitroamines **79** after the N-O bond was cleaved by reduction. Even though the reaction worked well for alkyl nitroalkenes, it failed for *β*-nitrostyrenes due to degradation of the products by retroaddition.



Scheme 36. The first organocatalytic hydroxylation of nitroalkenes

Very recently, Chen and co-workers described the enantioselective 1,4-addition of oxime **80** to trisubstituted *β*-nitroacrylates **81** to yield enantioenriched tertiary alcohols **82**, using cinchona alkaloids as the chiral catalyst.[56] The reaction had a wide scope and the products **82** were obtained in good yields and excellent enantioselectivities (Scheme 37). The *S* stereochemistry of the newly formed chiral centre was confirmed by X-ray crystallography, while cleavage of the N-O bond afforded aminoalcohol **83** in a good yield and without loss of *ee*. The authors found that thiourea catalysts were less enantioselective in this reaction, while they argued that the free OH group in the catalyst was involved in the mechanism as it hydrogen-bonds to the nitroalkene activating it.

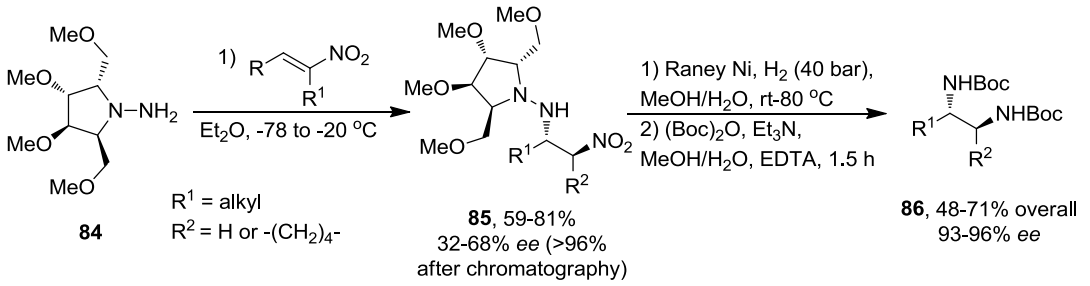


Scheme 37. An organocatalytic 1,4-addition of oximes

1.2.4 1,4-Additions of Nitrogen nucleophiles

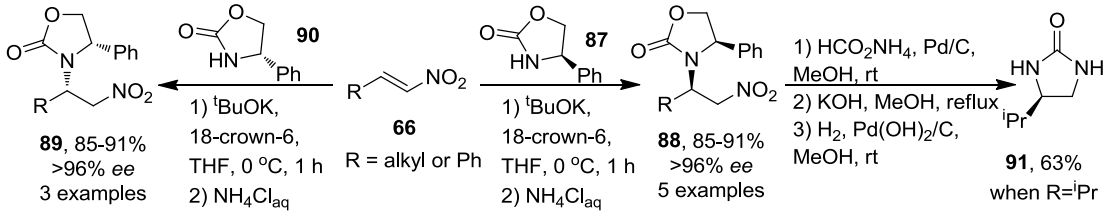
As with oxygen nucleophiles, a large number of reports also exist for the 1,4-addition of nitrogen nucleophiles to nitroalkenes. The asymmetric aza-Michael additions were based on either chiral auxiliaries or the use of a chiral catalyst.

Enders and Wiedemann reported the stereoselective synthesis of vicinal diamines by the conjugate addition of a chiral equivalent of ammonia, ADMP **84**.[57] The product *β*-nitroamines **85** were isolated in good yields and selectivities. Subsequent reduction and Boc protection gave the protected diamines **86** in good overall yields and excellent *ee* (Scheme 38).



Scheme 38. An auxiliary controlled aza-Michael addition

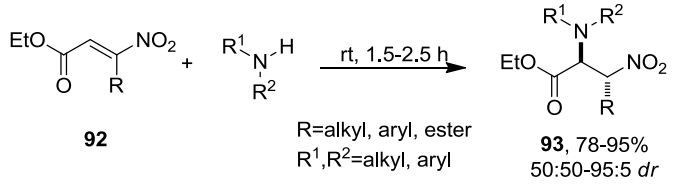
Another chiral auxiliary used in an asymmetric aza-Michael addition to nitroalkenes was chiral oxazolidinone **87** developed by Le Gall and co-workers (Scheme 39).[58] It was shown that the desired *β*-nitroamines **88** could be obtained in medium yields but high *ee*. Even though the scope of the reaction was limited, it was also possible to obtain the opposite enantiomers **89** by using *S*-oxazolidinone **90** as the nucleophile. Moreover, nitroamine **88** could be easily transformed to imidazolidinone **91**, though the chiral auxiliary could not be recovered.



Scheme 39. The aza-Michael addition of a chiral oxazolidinone

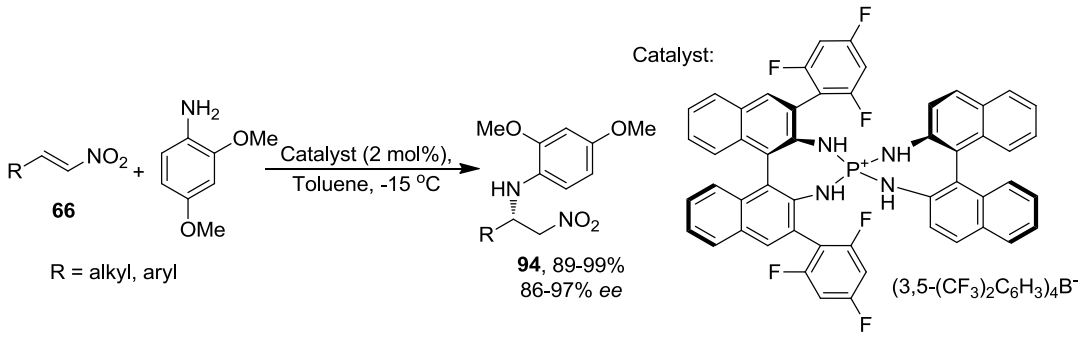
A diastereoselective-only example of the 1,4-addition of amines to nitroacrylates was reported by Ballini and co-workers in 2008.[59] The authors reported that one equivalent of amine reacted with one equivalent of nitroacrylate **92** at room

temperature in the absence of any solvent or catalyst (Scheme 40). Good yields of the product *β*-nitro-*α*-amino esters **93** were obtained, however in most cases with low diastereoselectivity.



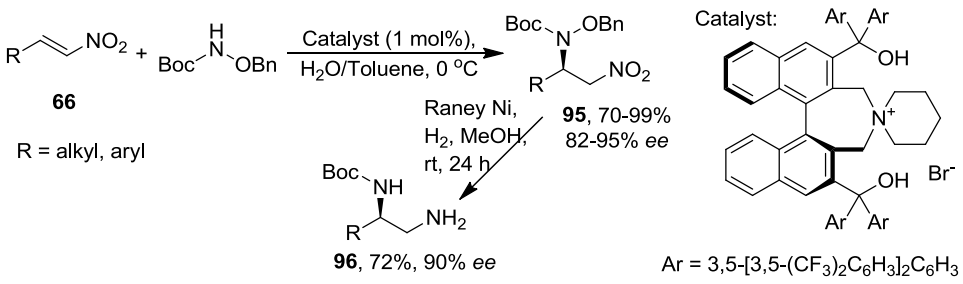
Scheme 40. A diastereoselective conjugate addition of amines to nitroacrylates

Recently, two reports appeared of catalytic asymmetric aza-Michael reactions to nitroalkenes. Ooi and co-workers reported the use of a chiral Brønsted acid catalyst to afford the asymmetric 1,4-addition of 2,4-dimethoxyaniline to nitroalkenes **66** (Scheme 41).[60] The product *β*-nitroamines **94** were isolated in excellent yields and *ee*.



Scheme 41. A chiral Brønsted acid catalysed 1,4-addition of amines

Maruoka and co-workers reported a catalytic asymmetric amination reaction of nitroalkenes using a chiral ammonium salt catalyst, under biphasic conditions.[61] The reaction gave nitroamines **95** in good yields and *ee* (Scheme 42), with alkyl nitroalkenes giving lower *ee*s (82-83% *ee*) than aromatic ones (91-95% *ee*). Catalyst loadings as low as 0.05 mol % were effective in most cases, however higher loadings (1 mol%) were needed for some "problematic" analogues. The absolute stereochemistry of the products was confirmed by conversion to the known diamine **96**.



Scheme 42. A chiral phase transfer catalysed 1,4-addition of amines.

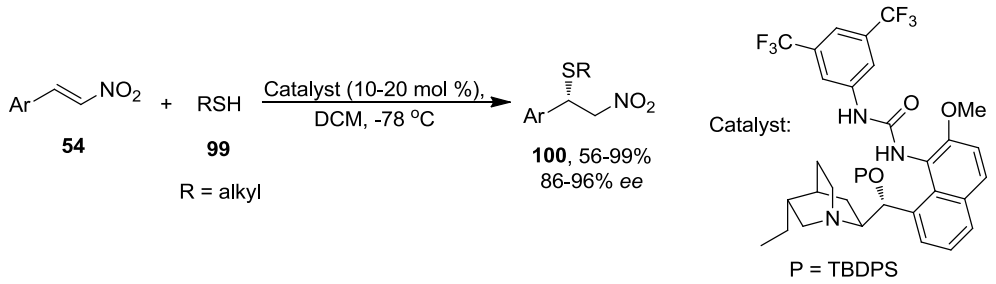
1.2.5 Miscellaneous 1,4-Additions

The conjugate additions of sulfur and phosphorus nucleophiles to nitroalkenes have also been widely reported. Focusing on sulfur nucleophiles, two publications stand out on the asymmetric additions of thiols to nitroalkenes, by Kobayashi and Connon, both using organocatalysis.

Kobayashi reported in 1981 the asymmetric conjugate addition of thioglycolic acid **97** to nitroalkenes **66** in the presence of a cinchona alkaloid catalyst (Scheme 43).[62] The reaction had a limited scope and low enantioselectivity. Moreover, the *ee*s of all products **98** were not reported and the reaction was not catalytic as 1 equivalent of quinine was required. The authors argued that the ionic interaction between the carboxylic acid in **97** and the tertiary nitrogen in the catalyst was responsible for the asymmetric induction.

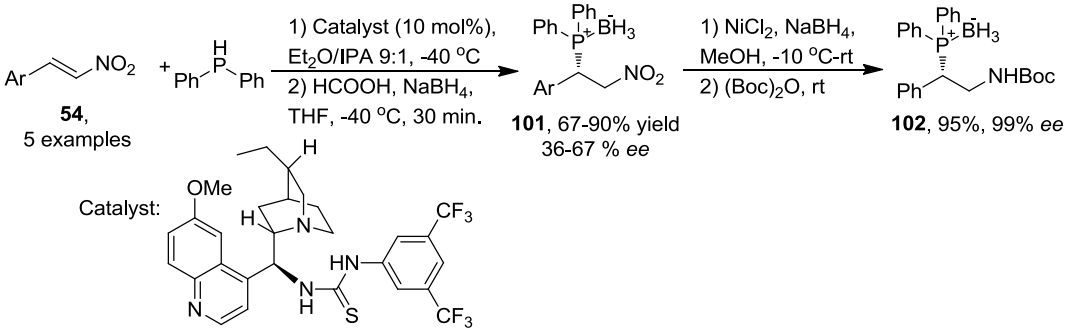
Scheme 43. Cinchona alkaloid catalysed asymmetric Michael addition of thiols.

Recently, Connon reported the asymmetric 1,4-addition of alkane thiols **99** to *β*-nitrostyrenes **54**, catalysed by a cinchona alkaloid-derived catalyst (Scheme 44).[63] The product sulfides **100** were isolated in good yields and *ee* and the reaction showed good scope as it worked well for electron rich or deficient, as well as heterocyclic nitrostyrenes.



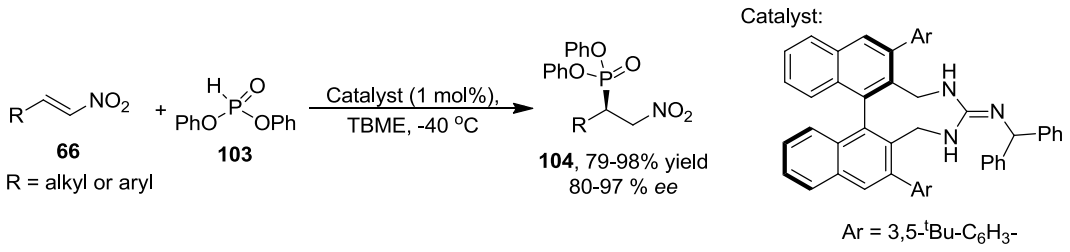
Scheme 44. Another organocatalytic conjugate addition of thiols

Organocatalysis was also used for the asymmetric conjugate additions of phosphorus nucleophiles. Melchiorre and co-workers first reported the asymmetric hydrophosphination of nitroalkenes **54**, catalysed by a bifunctional cinchona alkaloid and thiourea organocatalysts (Scheme 45).[64] This investigation was limited in scope and the observed *ee*s were modest, however the authors showed that the phosphine products could be protected by forming borane complexes **101** and converted to aminophosphines like **102**, which are potentially useful as chiral ligands. Moreover, the absolute stereochemistry of the products was confirmed by X-ray crystallography.



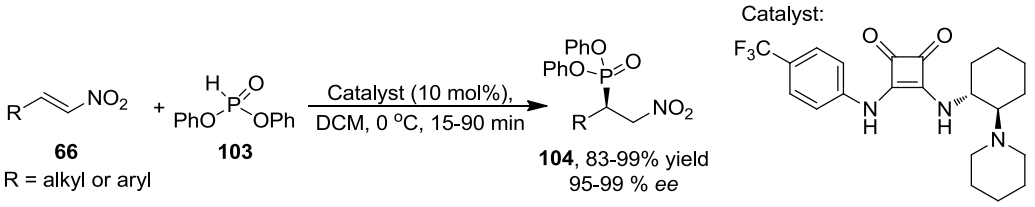
Scheme 45. The organocatalytic conjugate addition of phosphines to nitroalkenes

The 1,4-addition of phosphite **103** to nitroalkenes **66** using a chiral Brønsted base catalyst was reported by Terada and co-workers.[65] The reaction gave enantioenriched phosphites **104** in good yields and *ee*, while low catalyst loadings were required (Scheme 46).



Scheme 46. The asymmetric Michael addition of phosphites

Recently, Rawal and co-workers reported a new diamine-based catalyst for the asymmetric 1,4-addition of phosphite **103** to nitroalkenes **66**.[66] The reaction was fast, with broad scope and gave excellent yields and *ee*s of the desired products **104** (Scheme 47). The authors suggested that the squaramide catalyst works by hydrogen-bonding to the nitro group of the nitroalkene, which then obstructs one side of it to nucleophilic attack.



Scheme 47. A squaramide catalysed 1,4-addition of phosphites

1.2.6 Summary

Having briefly reviewed the literature of the asymmetric 1,4-additions to nitroalkenes, it is clear that the reaction is very general, as a wide variety of different nucleophiles have been shown to add to nitroalkenes. Moreover, a variety of asymmetric methods exist for performing these reactions to obtain enantioenriched α-substituted nitroalkanes. This shows that there is great potential on using those 1,4-additions to provide the nitroalkane or nitronate partner of the nitro-Mannich reaction. By performing the 1,4-addition reaction asymmetrically, it would be expected that the nitro-Mannich reaction would also be rendered asymmetric, thereby offering control over the stereochemistry of three consecutive stereocentres.

The tandem conjugate addition/nitro-Mannich reaction of Superhydride® and dialkylzincs has been studied by the Anderson group and will also be described in this thesis. The conjugate addition/nitro-Mannich reaction of other nucleophiles, both carbon and heteroatom, the Michael additions of which were discussed above, will also be portrayed in this thesis. Our investigation expands into the synthesis of more diverse molecules using the nitro-Mannich reaction. It is therefore required to describe the reported synthetic applications of the nitro-Mannich reaction.

1.3 Synthetic applications of the nitro-Mannich reaction

As a C-C bond forming reaction, the nitro-Mannich reaction offers a wide variety of synthetic applications. The usability of the reaction lays in the fact that it allows the synthesis of *β*-nitroamines, compounds that have two adjacent nitrogen substituents in different oxidation states. The nitro group in particular, is extremely versatile, described by Seebach as a "chemical chameleon" as it can be transformed to other functional groups (Figure 1).[67] A number of these modifications are described in the following section.

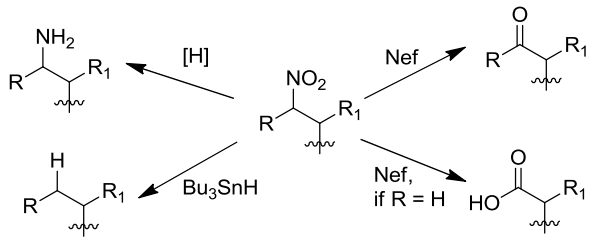
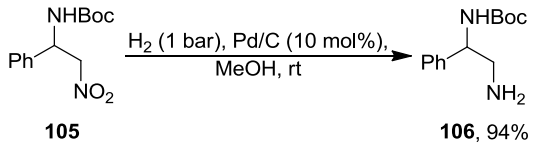


Figure 1

1.3.1 Functional group modifications-Nitro group reduction

The most widely used modification of the nitro group is its reduction to the corresponding amine. As it was seen in sections 1.1 and 1.2, the reduction of the nitro group frequently follows any reactions giving unstable nitroalkanes or *β*-nitroamines. The main reduction protocols reported were hydrogenation, hydride reduction and single electron transfer.

One example of a hydrogenation protocol, using Pd/C was reported by Palomo and co-workers.[68] The authors reduced *β*-nitroamine **105** using only an atmospheric pressure of hydrogen at rt to give diamine **106** in excellent yield (Scheme 48).

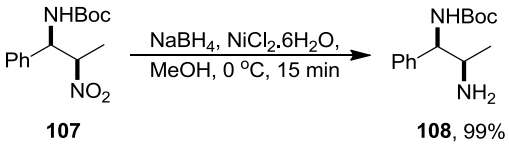


105 **106**, 94%

Scheme 48. Hydrogenation of the nitro group

Hydride reduction is one of the most widely used methods for the reduction of nitro compounds. Usually, the combination of $NaBH_4$ with a transition metal salt is used to form a more reactive metal boride species. Cobalt boride was used extensively by Johnston and co-workers for the reduction of nitroamines,[32] while nickel boride was

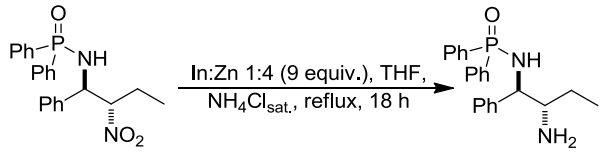
used by Dixon,[54] Melchiorre[64] and others for the reduction of a variety of *β*-nitroamines. One example of a nickel boride reduction is reported by Shibasaki who reduced nitroamine **107** to diamine **108**, fast and in excellent yield without any epimerisation (Scheme 49).[26]



107 **108**, 99%

Scheme 49. Nickel boride reduction of a nitro group

Another method of nitro group reduction is the dissolving metal reduction or single electron transfer. Some methods used are the SmI_2 reduction reported by the Anderson group (Section 1.1.3, Scheme 5),[13] the Zn/AcOH reduction developed by Feng and co-workers,[69] the Al/Hg method used by the Anderson group[37] and the In/Zn method reported by Ricci and co-workers.[70] The latter method was used to reduce nitroamine **109** to diamine **110** in good yield and with no epimerisation. The method was tolerant to the presence of a phosphine oxide group which was not reduced (Scheme 50).

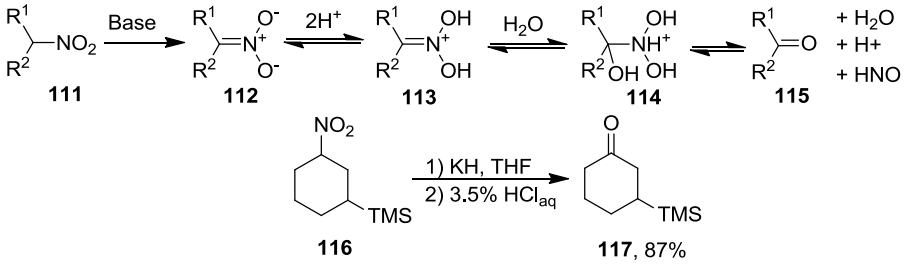


109 **110**, 92%

Scheme 50. A dissolving metal reduction of the nitro group

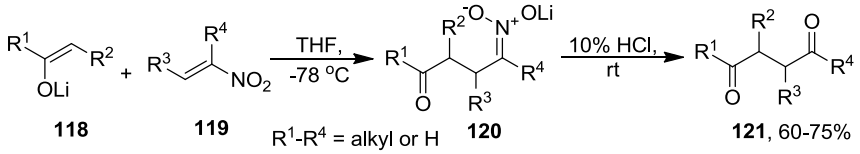
1.3.2 Functional group modifications-Nef reaction

After its discovery by Nef in 1894,[71] the conversion of nitroalkanes to ketones has been extensively employed in synthesis.[72] The original procedure included the treatment of nitro-compound **111** with a base, forming the nitronate anion **112**, followed by acid that gave the protonated form **113** (Scheme 51). Addition of water gave **114** that decomposes by losing hyponitrous acid and water to give carbonyl compound **115**. This method has been applied numerous times in synthesis and one example of it is the conversion of nitroalkane **116** to cyclohexanone **117** reported by Hwu and Gilbert.[73]



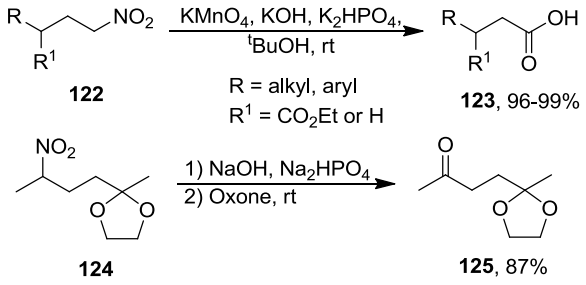
Scheme 51. Nef reaction by a base/acid treatment of nitroalkanes

The reaction can also be used in tandem syntheses such as that reported by Yoshikoshi and co-workers.[74] The authors reported the Michael addition of enolate **118** to nitroalkene **119** to give nitronate **120**, which after treatment with acid afforded diketones **121** (Scheme 52).



Scheme 52. The synthesis of diketones *via* a Nef reaction

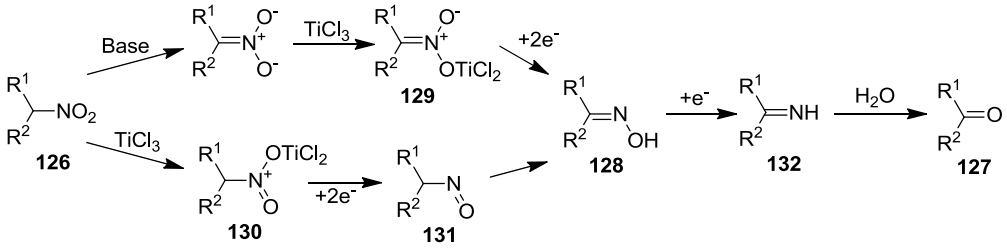
A variety of oxidative Nef reactions were also reported. Treatment of primary nitroalkanes **122** with a buffered $KMnO_4$ solution (pH=11) can oxidise them to the respective carboxylic acids **123** in good yields, as reported by Savilles-Stones and Lindell (Scheme 53).[75] Oxone was also used in oxidative Nef reactions and was shown to not affect common protecting groups like TBS ethers, acetals and acetates. In the example shown below, nitroalkane **124** could be transformed to ketone **125** in good yield (Scheme 53).



Scheme 53. Some oxidative Nef reactions

Finally, a variety of reductive Nef reactions have also been reported, mostly using a single electron transfer methodology. One of the most frequently used procedures is the McMurry method that uses $TiCl_3$.[76] The method was used to convert nitroalkanes

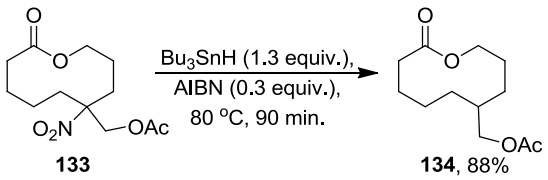
126 to aldehydes and ketones **127** and is thought to proceed *via* the intermediate oxime **128**. The oxime is formed either by reduction of titanium nitronate **129** or by reduction of ion **130** to nitroso compound **131**, followed by tautomerisation. The oxime is then reduced to imine **132**, which is hydrolysed to carbonyl compound **127** (Scheme 54).



Scheme 54. The mechanism of the $TiCl_3$ Nef reaction

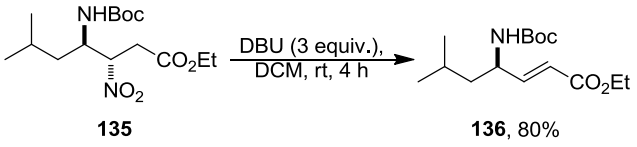
1.3.3 Functional group modifications-Denitration

The nitro-group is not usually present in many natural molecules and pharmaceutical compounds, therefore methods for its removal (denitration) are very desirable. A very popular method is radical denitration using Bu_3SnH and an initiator that affects the replacement of the nitro group by a proton. An example of this method is the radical denitration of macrolide **133** to **134**, developed by Ono and co-workers (Scheme 55).[77]



Scheme 55. Radical denitration with Bu_3SnH

Another method of denitration is the elimination of HNO_2 from nitroalkanes where the nitro group is adjacent to an electron-withdrawing group by treatment with base.[78] One example of this reaction is the reaction of *β*-nitroamines **135** with DBU to give *α,β*-unsaturated esters **136** in good yields, developed by Palomo and co-workers (Scheme 56).[31]

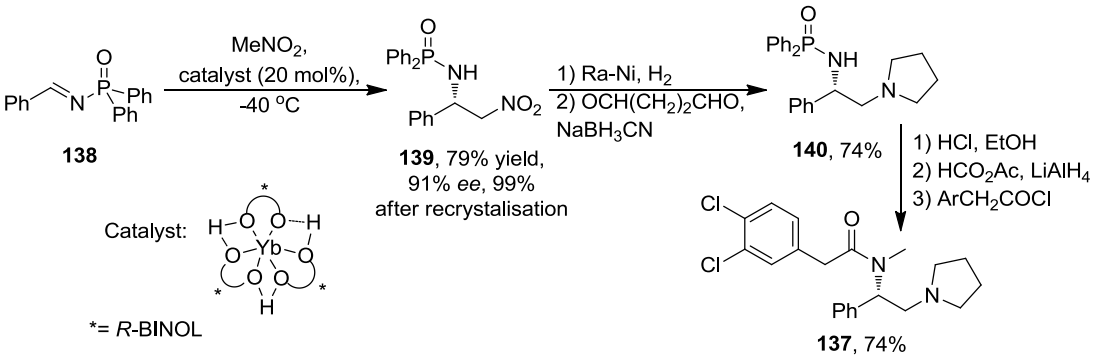


Scheme 56. Ionic denitration with DBU

1.3.4 Synthesis of natural products

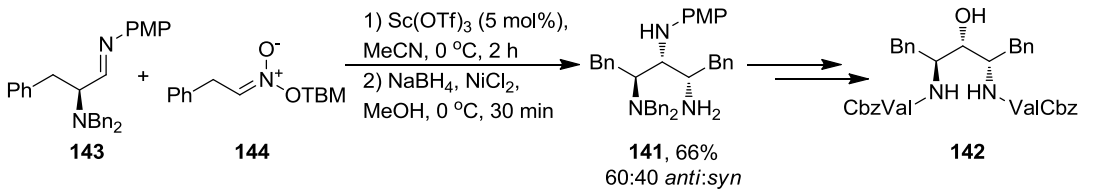
After the developments of the last two decades, the nitro-Mannich reaction has become an efficient and selective method to synthesise *β*-nitroamines.[79] The development of the reaction along with the many functional group modifications that could be performed on these products, renders it very useful in the synthesis of complex molecules leading to pharmaceuticals or biologically active natural products.

The nitro-Mannich reaction was first used in synthesis by Shibasaki and co-workers in the synthesis of the pharmaceutical molecule ICI-199441 (**137**),[80] which was found to be an opioid agonist.[81] The first step in the synthesis was the nitro-Mannich reaction of *N*-phosphinoyl imine **138**, catalysed by the metallic complex developed before,[19] that gave *β*-nitroamine **139** in good yield and excellent *ee* (Scheme 57). A subsequent hydrogenation and reductive alkylation gave pyrrolidine **140**, which could easily be converted to the desired compound **137** in an overall yield of 44%.



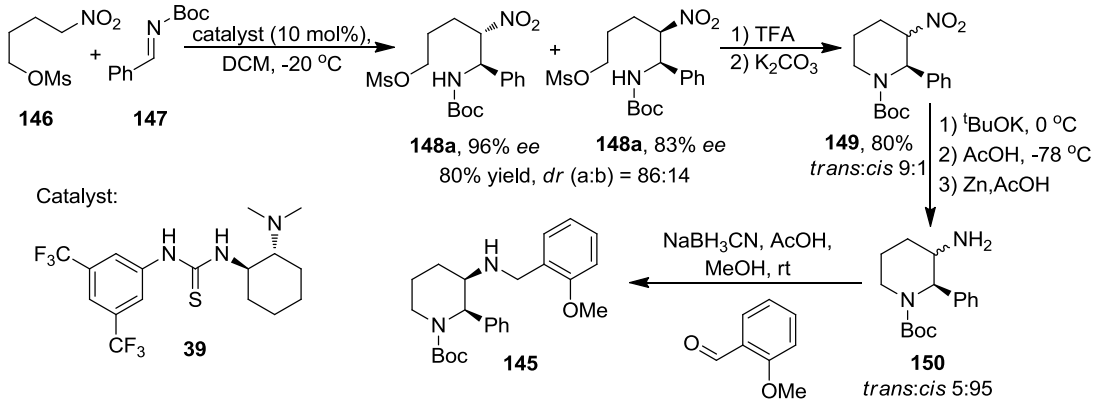
Scheme 57. The synthesis of ICI-199441

Bernardi and co-workers used the nitro-Mannich reaction to synthesise *pseudo*-C_2-symmetric triamines **141** which were precursors to HIV inhibitor A-74704 (**142**) (Scheme 58).[82] Reaction of chiral imine **143** with silyl nitronate **144** in the presence of a Lewis acid gave, after reduction with nickel boride, triamine **141** in 66% yield but with a poor *dr*.



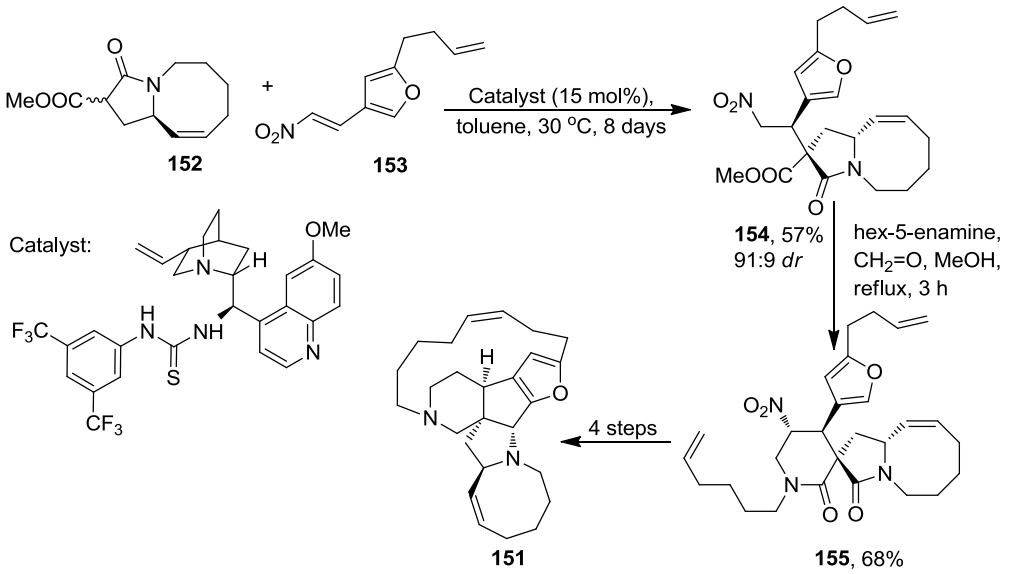
Scheme 58. The synthesis of HIV inhibitor **142** *via* a nitro-Mannich reaction

Takemoto and co-workers later reported the synthesis of potential antiemetic CP-99994 (**145**),[83] using a nitro-Mannich reaction as the first step.[84] The synthesis started from the reaction of nitroalkane **146** with imine **147** in the presence of thiourea catalyst **39**, which gave nitroamines **148a** and **148b** in good yield and *ee*, but medium *dr* (Scheme 59). Cyclisation then gave mainly *trans*-**149** that was epimerised and reduced to *cis*-**150**. A further reductive amination step afforded the desired diamine **145** in a very efficient 48% overall yield.



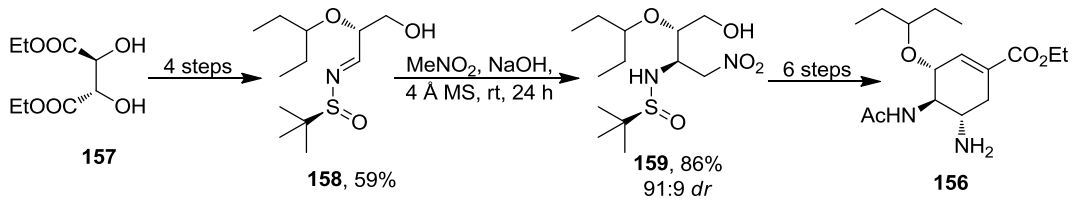
Scheme 59. The synthesis of CP-99994

Dixon and co-workers recently published the synthesis of (-)-Nakadomarin A (**151**), a marine alkaloid that showed anticancer and antimicrobial activity.[85,86] The key steps in the synthesis were the Michael addition of the ester enolate of **152** to nitroalkene **153** that gave nitroalkane **154** in medium yield and good *dr*, followed by a nitro-Mannich reaction with an *in situ* formed imine to give product **155** in good yield and excellent *dr* (Scheme 60). The two fragments **152** and **153** were synthesised in six and four steps respectively in 24% and 22% yields. Four further steps involving a radical denitration and an alkene methathesis reaction concluded the synthesis to give the natural product in 0.8% overall yield with the longest linear sequence being 12 steps.



Scheme 60. Dixon's synthesis of (-)-Nakadomarin A

Finally, Lu and co-workers reported the synthesis of oseltamivir (**156**), the active ingredient of the famous anti-influenza drug Tamiflu.[87,88] The synthesis started from natural diethyl D-tartate **157** and involved an enantioselective nitro-Mannich reaction of imine **158** bearing a chiral sulfoxide protecting group with nitromethane. The nitro-Mannich reaction gave *β*-nitroamine **159** in good yield and *dr* (Scheme 61). The synthesis was completed with six further steps to give **156** in 21% overall yield.



Scheme 61. Lu's synthesis of Oseltamivir

1.4 Stereoselective synthesis of piperazinones

As can be observed from the previous section, a number of biologically interesting natural products and pharmaceuticals, like CP-99994 and Oseltamivir, contain vicinal diamines. The synthesis of vicinal diamines using a nitro-Mannich reaction and their use in the synthesis of a natural product is the subject of part of the research described in this thesis (section 2.6). This section will therefore discuss briefly the importance of 1,2-diamines and concentrate on piperazin-2-ones and the methods for their preparation.

1.4.1 Vicinal diamines

The 1,2-diamine motif is found in a variety of biologically active molecules, both natural and synthetic ones. Furthermore, this functional group has found numerous applications in asymmetric synthesis, as 1,2-diamines are often the source of chirality in many chiral catalysts, both metallic (as ligands) and organometallic ones. Some examples of biologically active diamines include biotin **160** (vitamin B_7), Penicillin antibiotics **161** and the protein kinase inhibitor balanol **162** (Figure 2).[89,90]

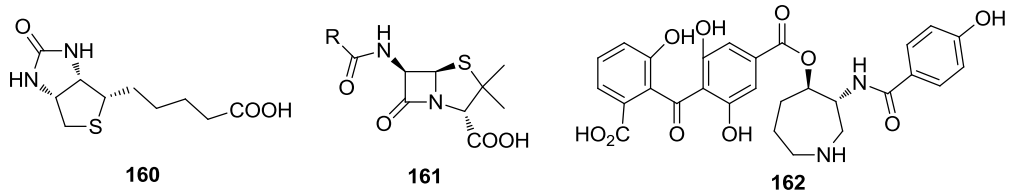


Figure 2. Some biologically active 1,2-diamines

1.4.2 Biologically important piperazin-2-ones

A very useful group of compounds that contains the 1,2-diamine motif are piperazin-2-ones. The related piperazines, are found in a great number of drug molecules, specifically those with substitution only on the nitrogen atoms, due to the starting material being piperazine. Some examples include the antihistamine drug Cyclizine (**163**), the antidepressant Amoxapine (**164**) and the anti-ischemic agent Trimetazidine (**165**) (Figure 3).

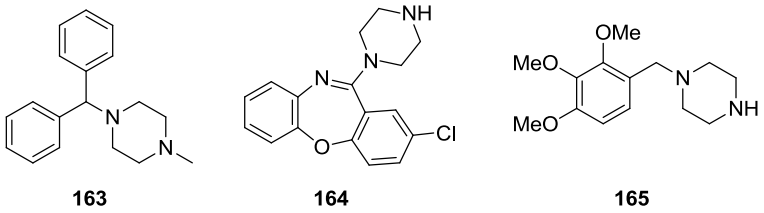
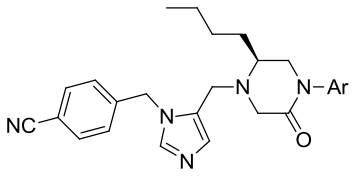


Figure 3. Drugs containing a piperazine moiety

Even though piperazin-2-ones are not as widely prevalent as piperazines in drug molecules, they frequently exhibit biological activity and are the object of many medicinal chemistry studies. Some of these investigations will be presented in this section.

When investigating the synthesis of farnesyltransferase inhibitors, Williams and co-workers found that piperazinones **166** were effective targets (Figure 4).[91] The enzyme

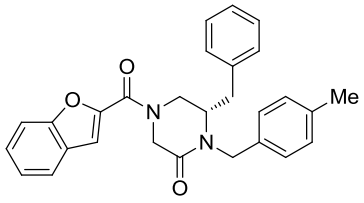
farnesyltransferase is responsible for the activation of Ras protein, a small protein that directly affects tumor growth. This new class of inhibitors showed an inhibition of tumor growth in rats bearing H- or K-ras-dependent tumors.



166

Figure 4

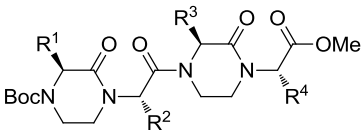
More recently, Boger and co-workers investigated piperazinones **167** as inhibitors of the hemorrhagic fever arenavirus Lassa (LASV).[92] After a screening of a large library of compounds, the authors identified the (-)-enantiomer of **167** as the most active, which after asymmetric synthesis was found to be (*S*)-**167** (Figure 5).



167

Figure 5

Arora and co-workers investigated oligo-oxopiperazines as non-peptide mimetics of protein α-helixes.[93] The authors used circular dichroism and NMR spectroscopy to conclude that oligooxopiperazine dimers **168** adopt conformations that resemble the peptide chain arrangement of an α-helix (Figure 6). Such scaffolds are very valuable tools in chemical biology.[94]

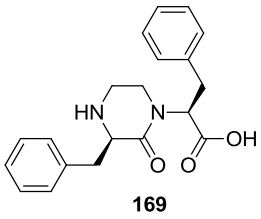


168, R^1-R^4 = alkyl

Figure 6

Jankowski and co-workers investigated the use of cyclic oligopeptides as analogues of cyclosporine A, a known immunosuppressant drug.[95] The authors reported that when

piperazinone **169** was used instead of a Phe-Phe dipeptide linkage, the synthesised peptides showed increased immunosuppressive activity (Figure 7).



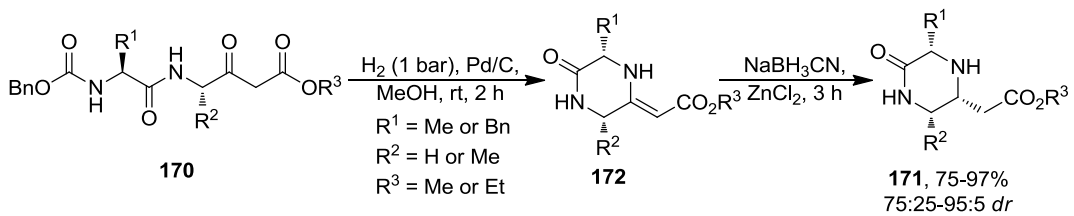
169

Figure 7

1.4.3 Synthesis of piperazin-2-ones

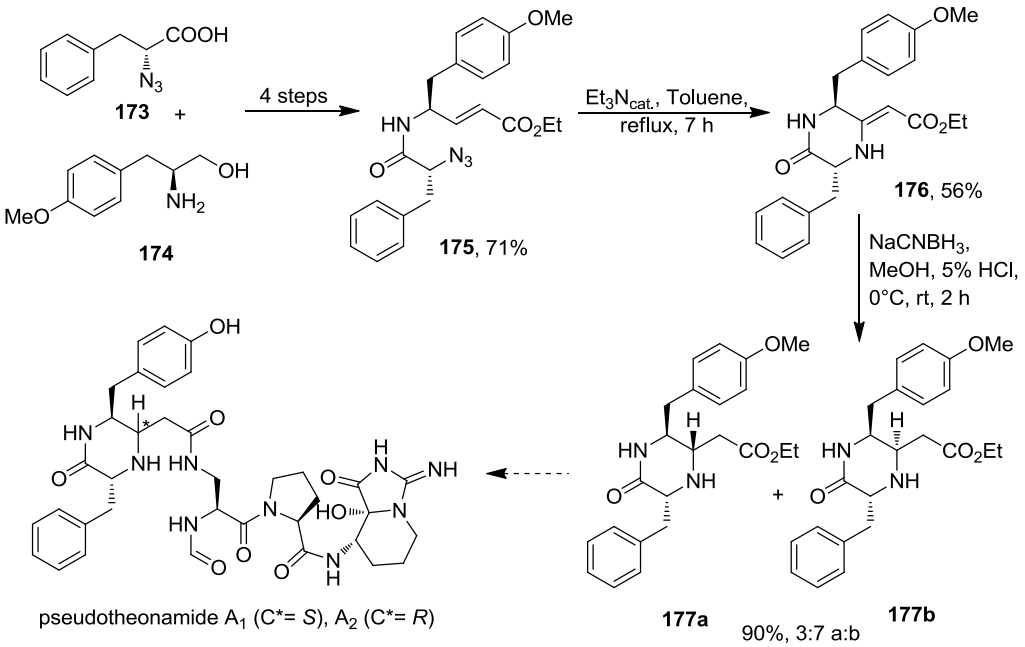
As was seen in the previous section, piperazinones are useful compounds and are increasingly being used in drug design. Therefore, new methods to synthesise piperazinones are required. A few examples exist for the synthesis of multi-substituted piperazinones, that include formation of the ring system from condensation of 1,2-diamines with a suitable two-carbon synthon, by an intramolecular cyclisation from peptides and by an intramolecular [3+2] reaction of an azide.

Gonzalez-Muñiz and co-workers developed an intramolecular reductive amination of *β*-ketoesters **170** to prepare trisubstituted piperazin-2-ones **171** (Scheme 62).[96] The desired piperazinones were obtained in good yields and selectivity while enamine **172** was proposed as the reaction intermediate. The reaction could be performed in one step by using H_2 (3 bar), Pd/C and a temperature of 45 ^oC, however better selectivities were observed from the two step protocol using $NaBH_3CN$ (Scheme 62). According to this synthetic approach, different side chains could be incorporated in different positions of the piperazinone products by selecting the suitable dipeptide starting material.



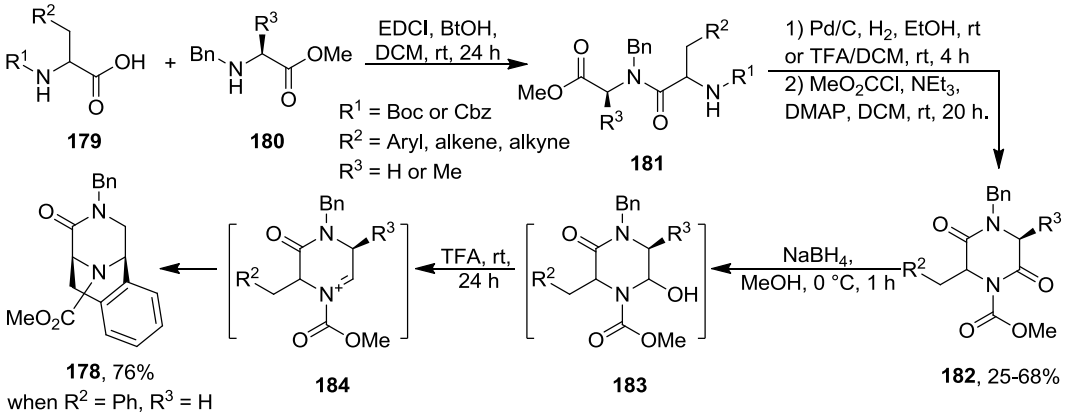
Scheme 62. Synthesis of piperazinones *via* an intramolecular reductive amination

Another synthetic route to piperazinones is by a [3+2] cycloaddition reaction developed by Gurjar and co-workers in their efforts towards the synthesis of serine protease inhibitors pseudotheonamide A_1 and A_2.[97] Starting from α-azidoacid **173** and aminoalcohol **174**, the authors could access amide **175** in good yield, which could then undergo a dipolar cycloaddition reaction followed by elimination of N_2 to give piperazinone **176** (Scheme 63). Subsequent reduction with cyanoborohydride gave the final product as a mixture of the two diastereoisomers **177a** and **177b**, both of which were useful for the synthesis of the two natural products.



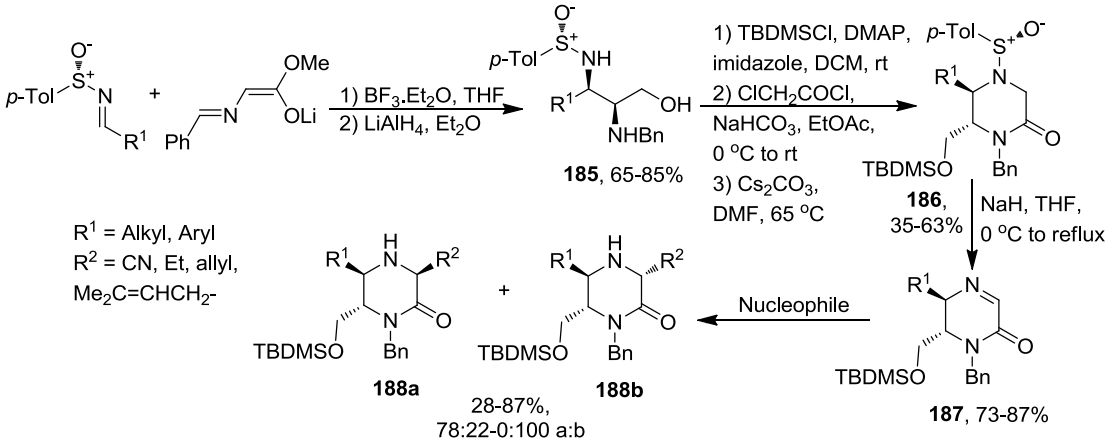
Scheme 63. Synthesis of piperazinones *via* a [3+2] cycloaddition reaction

Hiemstra and co-workers reported the synthesis of 2,6-bridged piperazine-3-ones **178**, starting from aminoacids.[98] Coupling of aminoacids **179** and **180** initially gave dipeptides **181** that after deprotection of the amine cyclised to piperazinediones **182**, protected as carbamates (Scheme 64). Subsequent chemoselective reduction of the C^6 carbonyl to hydroxylactam **183** and treatment with TFA led to formation of acyliminium species **184** that was trapped by the nucleophilic R^2 group. The final products, 2,6-bridged piperazin-2-ones like **178** were isolated in good yields. It is noted that by adjusting the absolute configuration of **179**, different diastereoisomers of the final product could be obtained.



Scheme 64. Synthesis of 2,6-bridged piperazine-3-ones

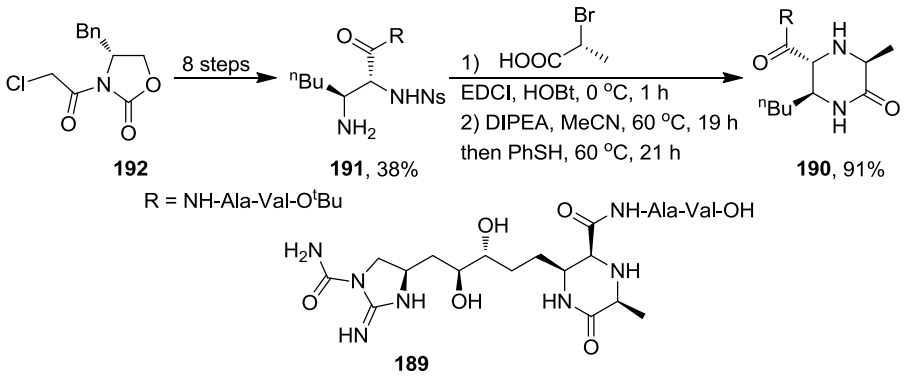
Viso and co-workers reported the asymmetric synthesis of *syn*-diamines **185** in good yields as a single diastereoisomer using a chiral sulfoxide moiety.[99] These diamines were used in a more recent publication in the synthesis of piperazin-2-ones. Subsequent treatment with α-chloroacetyl chloride and cyclisation gave piperazinones **186** in good yields (Scheme 65).[100] Treatment with NaH led to elimination of the sulfinyl group to afford imines **187**. The nucleophilic addition of a number of nucleophiles to imines **187** was then investigated. Variable yields and selectivities were observed with some nucleophiles favouring *anti*/*syn* diastereoisomer **188a** (Et_2Zn, 78:22 *dr*) and some *anti*/*anti* diastereoisomer **188b** (allylMgBr/$CeCl_3$, 0:100 *dr*). These diastereoselective alkylations showed that this method could be used to synthesise multi-functionalised piperazinones.



Scheme 65. Synthesis of piperazin-2-ones from vicinal diamines **185**

When investigating the absolute configuration of guadinomine C_2 **189** and related natural antibacterial agents, Sunazuka and co-workers developed an asymmetric synthesis for piperazin-2-one **190**.[101] Initially chiral diamine **191** was synthesised in

eight steps from chiral oxazolidinone **192** in 38% overall yield. Subsequent coupling with optically active 2-bromopropionic acid, followed by deprotection of the nosyl group, gave piperazin-2-one **190** in good yield (Scheme 66). This study showed that the correct absolute configuration of **189** is the one shown below.



Scheme 66. Synthesis of piperazin-2-one **190** from vicinal diamine **191**

1.5 Stereoselective syntheses of pyrrolidinones

Similar to piperazinones, pyrrolidinones are interesting synthetic targets due to their pharmacological properties and as precursors to other heterocycles. Many useful compounds contain the pyrrolidine-2-one moiety such as the dietary supplement pyroglutamic acid **193** and the nicotine metabolite cotinine **194** that is used as an antidepressant (Figure 8). Specifically, pyrrolidine compounds bearing a 1,2-diamine like **195** (Figure 8) have shown activity as proteasome and melanoma inhibitors.[102]

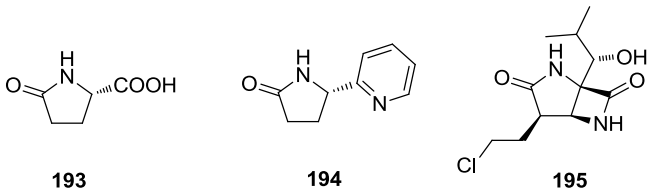
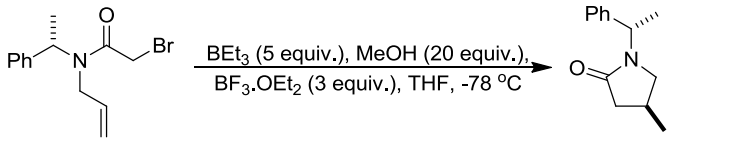


Figure 8. Biologically active pyrrolidinones

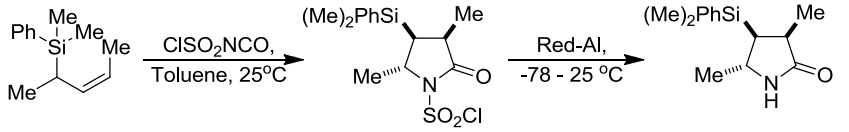
A variety of methods were reported in the literature for the synthesis of pyrrolidin-2-ones. A frequently used method is radical cyclisations, an example of which is the reaction of optically pure *N*-allyl-*α*-bromoacetamides **196** under tin-free conditions (Scheme 67).[103] Wood and co-workers have reported the use of BEt_3/H_2O as the radical initiator. The reagent works by liberating an ethyl radical after reaction with molecular oxygen.[104] The reaction gave good yields of 4-alkyl-pyrrolin-2-ones **197** *via* a 5-*exo*-trig radical cyclisation (Scheme 67).



196 **197**, 81%, 90:10 *dr*

Scheme 67. Synthesis of pyrrolidin-2-ones by a radical cyclisation

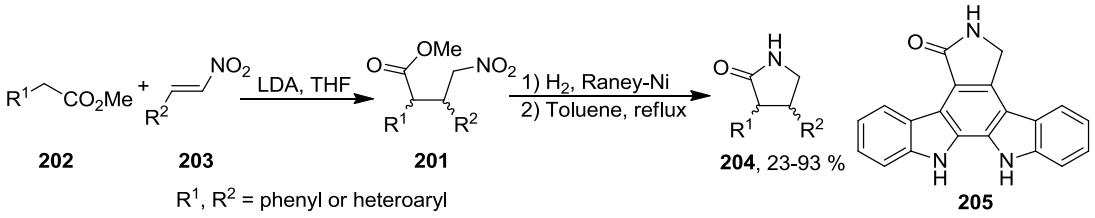
Furthermore, [3+2] cycloaddition reactions have been used in the synthesis of pyrrolidin-2-ones. Woerpel and co-workers reported a stereoselective synthesis of pyrrolidinones **198** *via* the [3+2] annulation of allylsilanes **199** and chlorosulfonyl isocyanates (Scheme 68).[105] Subsequent cleavage of the sulfinyl group gave pyrrolidinones **200** in good yields and *dr*.



199 **198** **200**, 68%, 92:8 *dr*

Scheme 68. A [3+2] cycloaddition reaction

Lactamisation also provided useful routes to the pyrrolidin-2-one ring system. Mahboobi and co-workers reported the synthesis of nitroesters **201** *via* an intermolecular Michael addition, starting from substituted acetate Michael donors **202** and nitroalkenes **203**. Subsequent reduction of the nitro group and cyclisation gave pyrrolidinones **204** albeit in variable yields and *dr* (Scheme 69).[106] This method was used for the synthesis of natural product Staurosporinone (**205**).

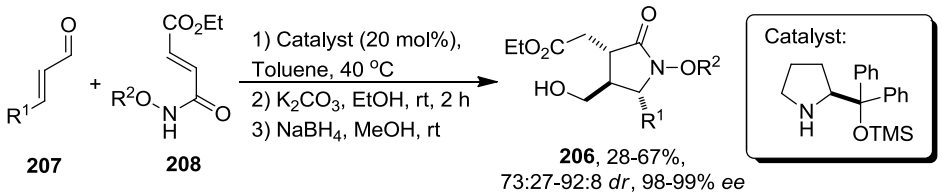


202 **203** **201** **204**, 23-93 % **205**

R^1, R^2 = phenyl or heteroaryl

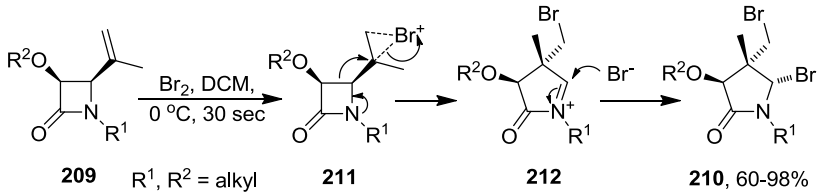
Scheme 69. Synthesis of pyrrolidin-2-ones *via* lactamisation

Recently, Hamada and co-workers reported the stereoselective synthesis of densely functionalised pyrrolidinones **206** by a cascade reaction of enals **207** with the both electrophilic and nucleophilic, fumaric acid amide esters **208** (Scheme 70).[107] A cascade aza-Michael/Michael reaction followed by epimerisation with K_2CO_3 and reduction with $NaBH_4$ gave pyrrolidinones **206** in variable yields but good selectivities.



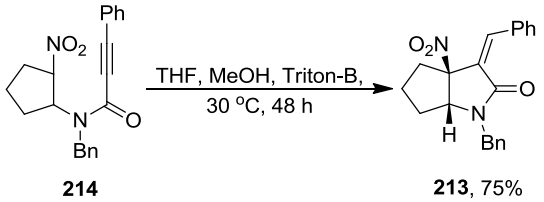
Scheme 70. Synthesis of pyrrolidinones *via* a cascade aza-Michael/Michael reaction

Perhaps more interesting is the synthesis of pyrrolidin-2-ones from ring expansion reactions of azetidin-2-ones. The reaction is driven by the release of strain of the four-membered ring, and has been frequently used in synthesis.[108] An example is the diastereoselective electrophile-induced ring expansion of 4-isopropenylazetidin-2-ones **209** towards 5-bromopyrrolidin-2-ones **210** (Scheme 71).[109] Treatment of **209** with bromine leads to electrophilic addition on the double bond to give bromonium cations **211**, which then ring expand to give *N*-acyliminium cations **212**. Subsequent nucleophilic addition of bromide affords pyrrolidinones **210** in good yield.



Scheme 71. Synthesis of pyrrolidinones *via* ring expansion

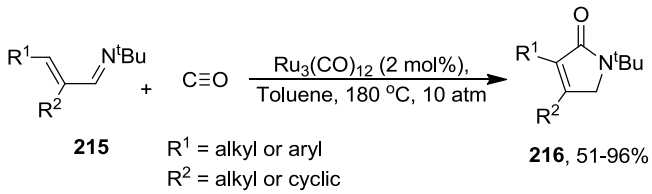
Another interesting method of making pyrrolidinones employs an intramolecular nucleophilic attack on a suitable electrophilic acceptor in the same molecule. Chatterjee and co-workers reported the stereoselective synthesis of 3-alkylidene pyrrolidinones **213** *via* a carbanion addition to acetylenes **214** (Scheme 72).[110]



Scheme 72. An intramolecular nucleophilic addition reaction

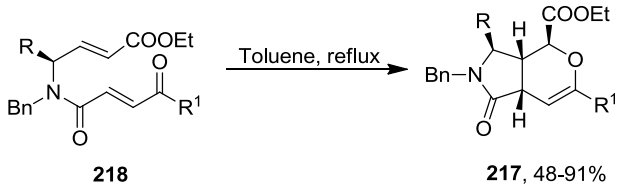
A more innovative synthesis of the related 1*H*-pyrrol-2(5*H*)ones **216**, applying organometallic chemistry was developed by Murai and co-workers using a catalytic carbonylative [4+1] cycloaddition on a 1,3-conjugated system catalyzed by

$Ru_3(CO)_{12}$.[111] In this synthesis, an α,β-unsaturated imine **215** reacted with CO to give compounds **216** in good yield (Scheme 73).



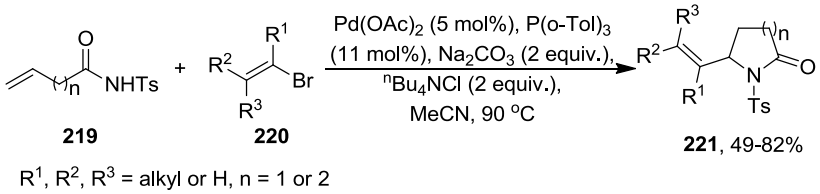
Scheme 73. A carbonylative [4 + 1] cycloaddition

An intriguing intramolecular oxo-Diels-Alder reaction has been developed by Murray and co-workers for the synthesis of multi-functionalised pyrrolidinones **217** (Scheme 74).[112] The resulting pyrrolidinones **217** were isolated as the *cis*-fused isomers in good yields and as single diastereoisomers. However the synthesis suffers from the need to use NH-Boc protected *L*-amino acids as the source of chirality in the starting materials **218**.



Scheme 74. An intramolecular oxo-Diels-Alder reaction

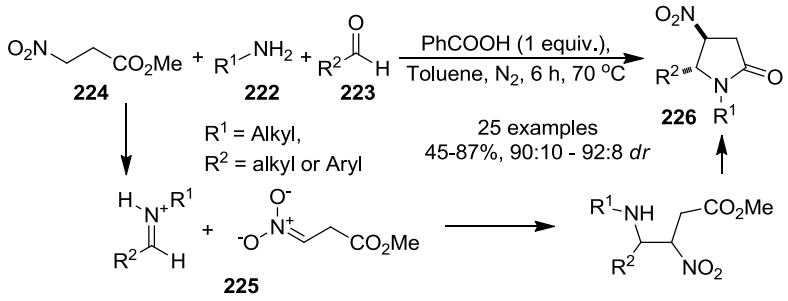
A novel route to pyrrolidinones *via* a tandem Heck-allylic substitution reaction was reported by Feringa and co-workers in 2003.[113] Reacting amides **219** with bromides **220** gave pyrrolidinones **221** in medium yields. After optimisation it was found that Na_2CO_3 was the best base and that the use of $^nBu_4NCl$ as a transfer reagent was required (Scheme 75). This method was also applied in the synthesis of piperidin-2-ones by the use of longer amides (n=2).



Scheme 75. A tandem Heck-allylic substitution reaction

Finally, a very recent and relevant synthesis of pyrrolidin-2-ones, is the one developed by Dixon and co-workers in 2009 that utilizes a nitro-Mannich reaction and a

lactamisation cascade.[11] In this three-component synthesis, amine **222**, aldehyde **223** and nitroalkane **224** (methyl 3-nitropropanoate) were heated in toluene leading to the *in situ* formation of an imine, that abstracted a proton from the nitroalkane to give ion pair **225**. The anion was then added to the imine followed by cyclisation to give pyrrolidinones **226** (Scheme 76). The reaction was broad in scope and highly diastereoselective and was also extended to cyclic imines allowing the direct formation of polycyclic pyrrolidinone derivatives. This synthesis shows that the nitro-Mannich reaction can be used efficiently to make pyrrolidinones with variable substituents that could be of use as building blocks in synthesis.



Scheme 76. Synthesis of pyrrolidinones *via* a nitro-Mannich reaction

As can be seen from the reported methods for synthesising pyrrolidinones, many of them are lengthy procedures, while others require starting materials that are expensive or hard to make. Moreover, while many syntheses are diastereoselective, only a few of them are enantioselective. Efficient syntheses of pyrrolidinones from simple starting materials, such as the last one presented (Scheme 76),[11] would be very useful for the preparation of important pyrrolidinones and the formation of many analogues necessary for possible biological testing of drug candidates. One new method of synthesising pyrrolidin-2-ones is discussed in this thesis, using a tandem 1,4-addition/nitro-Mannich/lactamisation reaction (section 2.2).

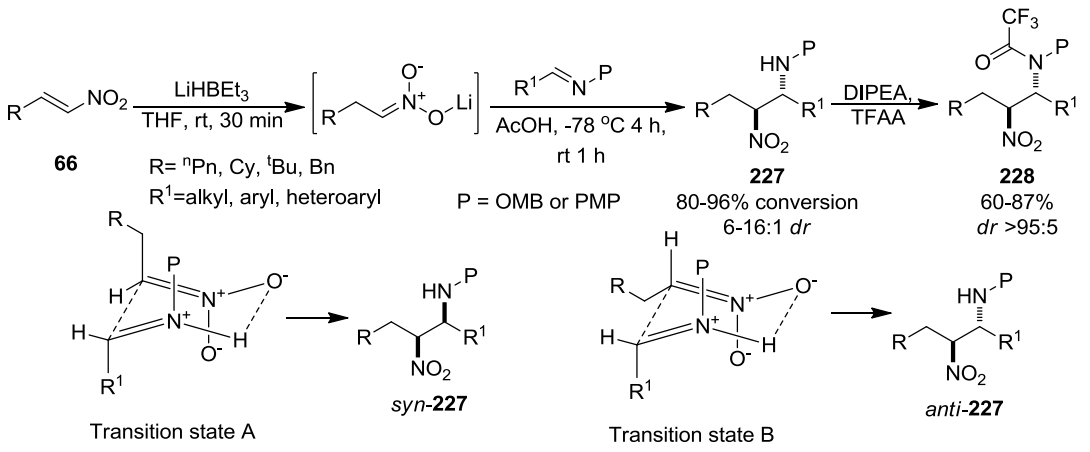
2. Results and discussion

2.1 Previous work and methodology

Recently, the Anderson group has started to investigate the use of nitroalkenes as precursors for the nitro-Mannich reaction. The 1,4-addition of nucleophiles to nitroalkenes can create reactive nitronate species that can subsequently react with imines in the nitro-Mannich reaction. The use of hydride ions and dialkylzinc species as nucleophiles has been investigated.[36,114]

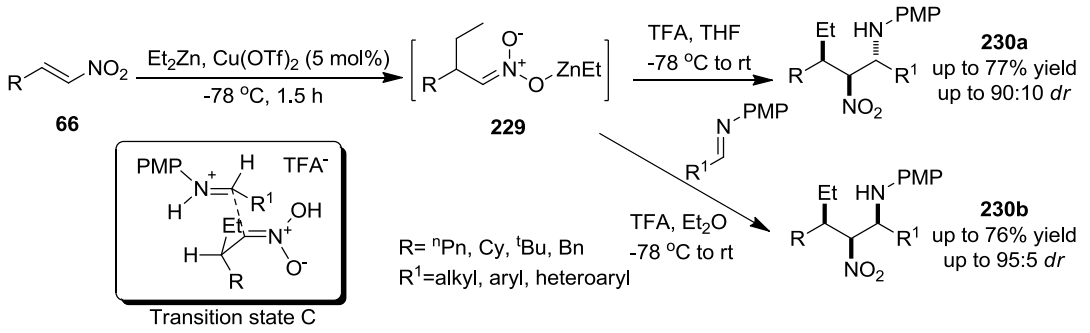
As shown in Scheme 77, a variety of nitroalkenes **66** can undergo a one-pot reductive nitro-Mannich reaction when they are reduced with Superhydride®, to form a nitronate ion. This can then react with OMB or PMP-imines in the presence of acetic acid. The acid is needed to activate the imine towards the reaction by making it more electrophilic. The *β*-nitroamines **227** were isolated in good yields and diastereoselectivities after being protected as the trifluoroacetamides **228**. This protection was necessary as the *β*-nitroamines were unstable to purification, due to retroaddition.

It was postulated that the nitro-Mannich reaction proceeds *via* a Zimmerman-Traxler type transition state, which explains the observed *anti* relative stereochemistry of **227**. Two possible transition states exist if we assume that the imine is fixed in the *E* geometry (Scheme 77). Transition state A, leading to the *syn* isomer, suffers from an unfavourable 1,3-diaxial interaction between the axial CH_2R group and the imine protecting group P (OMB or PMP). Transition state B leads to the *anti* isomer and does not suffer from such an interaction, making it more favourable.



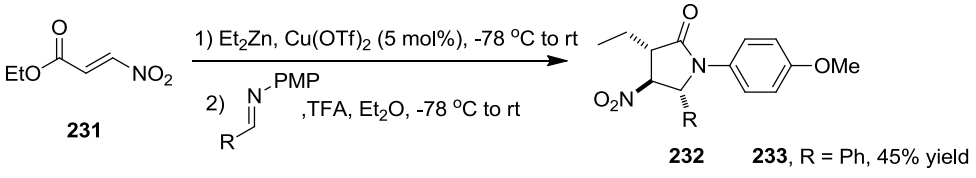
Scheme 77. A one-pot reductive nitro-Mannich reaction

Dialkylzinc reagents were also investigated. Diethylzinc was found to be a very effective reagent in the one pot 1,4-addition/nitro-Mannich reaction. The initial 1,4-addition of the ethyl group in the presence of $Cu(OTf)_2$ gave nitronate species **229** (Scheme 78). The nitronate then underwent a nitro-Mannich reaction giving, after protection with TFAA, highly-functionalised trifluoroacetamides **230a** and **230b**.[35] Interestingly, different diastereoselectivity was observed with different solvents, with THF giving mainly *syn/anti* diastereoisomers and Et_2O giving *syn/syn* diastereoisomers (Scheme 78). The cause of this selectivity was suspected to be the difference in solubility of $Zn(O_2CCF_3)_2$ in the two solvents. In the case of THF, the reaction mixture was homogenous and the selectivity could be explained from a metal centred "Zimmerman-Traxler" type transition state. With Et_2O, the reaction was heterogenous and was suspected to react *via* acyclic transition state C. The reaction worked best with PMP protected imines and could also be performed asymmetrically using chiral phosphine ligands in the 1,4-addition step to give highly enantioenriched products.[50,51]



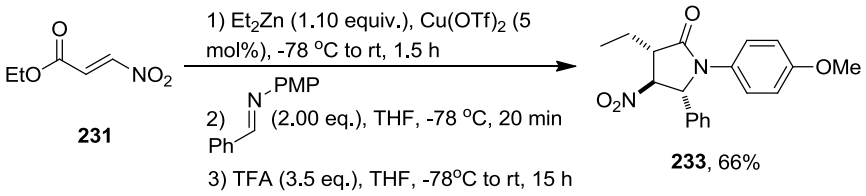
Scheme 78. A 1,4-addition/nitro-Mannich reaction with diethylzinc

During this work, it was discovered that by using nitroacrylate **231** as the nitroalkene, the *β*-nitroamine produced from the nitro-Mannich reaction subsequently cyclised to give highly functionalised pyrrolidinones **232**. When the reaction was attempted with PMP protected phenyl imine, the expected product **233** was isolated as a single diastereomer in 45% yield (Scheme 79).[115]



Scheme 79. Synthesis of pyrrolidinones **232** from nitroacrylate **231**

After optimisation it was found that the best conditions for the reaction were the use of THF as the solvent and the use of 1.10 equiv. of diethylzinc in the 1,4-addition step (found to be complete in 1.5 h). Also, the addition of excess imine (2.00 equiv.) and of 3.50 equiv. of TFA was found to be optimal, as well as a prolonged reaction time of 15 h. With all these improvements and the confirmation that the *para*-methoxyphenyl imine was the best for this reaction, the yield of phenyl substituted pyrrolidinone **233** reached 66% (Scheme 80).[116]



Scheme 80. Optimised condition for the synthesis of **233**

The reaction worked well with a variety of *ortho*, *meta* and *para* substituted aryl imines to give yields of 46-84% (Figure 9). The lowest yields were obtained for *ortho*-substituted aryl groups, presumably due to steric reasons. Single diastereoisomers were isolated in every case.

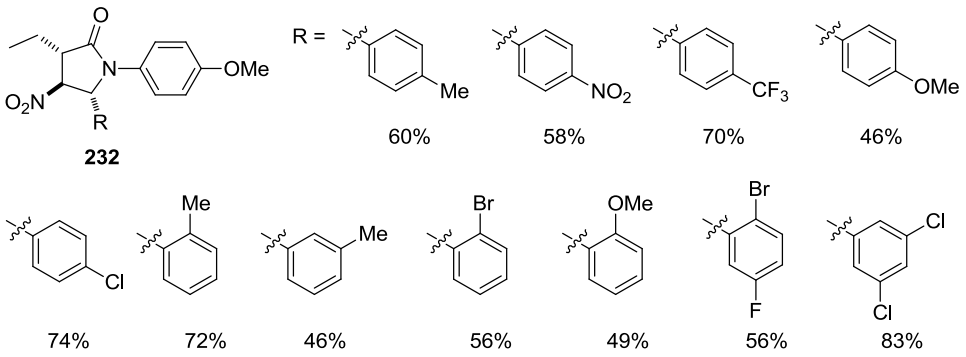


Figure 9

Alkyl analogues **234**-**238** were also made in yields of 38-69%, while the ^{t}Bu analogue **237** was isolated in only 19% yield. Dimethylzinc was proven to work just as well as diethylzinc, to give pyrrolidinone **242** (Figure 10). Moreover, **239**, **240** and **241** were the only heteroaryl analogues made in 64-70% yield, while no reaction occurred when 3-indole PMP protected imine was used. An initial effort to develop an asymmetric variant of the reaction was made using a phosphoramidite catalyst in the 1,4-addition step, which gave pyrrolidinone **233** in 52% *ee*, although the absolute stereochemistry was not determined.

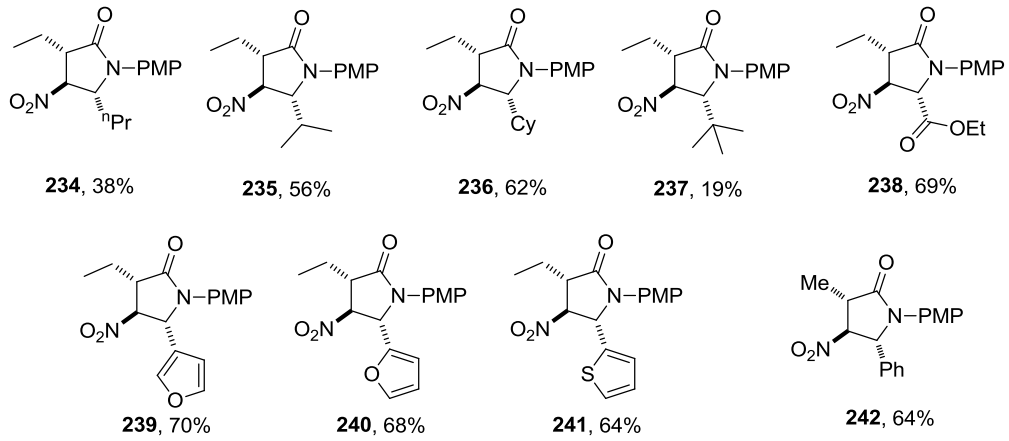
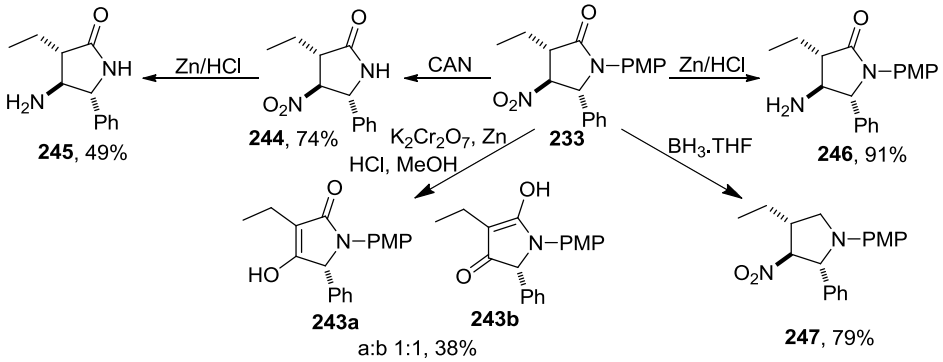


Figure 10

Furthermore, some additional functionalisation of the pyrrolidinone core was attempted. The successful functionalisations include removal of the PMP group from pyrrolidinone **233**, reduction of the nitro group to the corresponding amine and reduction of the amide group to an amine. However, some transformations were not so successful, such as the Nef reaction, which gave only 38% yield of pyrrolidinones **243a** and **243b** (Scheme 81).



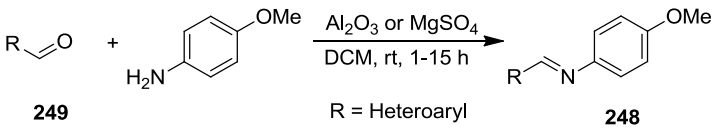
Scheme 81. Functionalisations of pyrrolidinone **233**

2.2 Proposed research

It was apparent that some further investigation of this reaction and of the functionalisation of the products was needed. The proposed research was to expand on the existing results and develop a more efficient asymmetric synthesis of these densely functionalised pyrrolidinones, in order to exploit its use in natural product synthesis.

The study would focus on functionalisation of the general structure **233** (Scheme 81) where the substituents can be varied. Variation of the R group derived from the

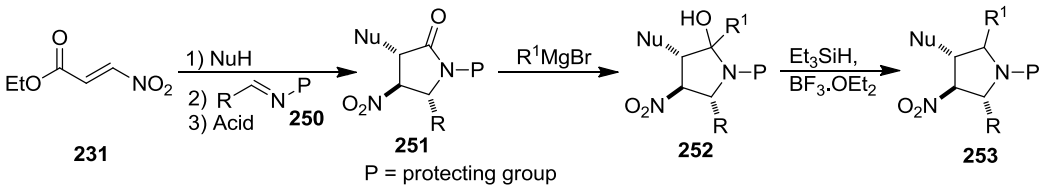
starting imine had been studied in some depth. However, some gaps remained such as the fact that no nitrogen containing heterocyclic imines had been used successfully. Various heterocyclic imines **248** can easily be accessed from the corresponding aldehydes **249** *via* a simple condensation with *para*-anisidine, in the presence of a suitable dehydrating agent (Scheme 82).



Scheme 82. Synthesis of *N*-PMP imines

The other variable that we wished to investigate was the type of nucleophile that could be used in this process. Previously only an ethyl nucleophile from diethylzinc had been used, however the presence of an ethyl group is rare in naturally occurring pyrrolidines and it is not versatile as it cannot be removed, modified or substituted. Some other diorganozinc reagents can be accessed using a combination of $Zn(OMe)_2$ and Grignard reagents, as reported by Charette.[117] Perhaps more interesting would be the use of O and N nucleophiles like the ones mentioned in section 2.5. Successful use of these nucleophiles (NuH) and a suitable imine (**250**), would be beneficial as it would allow the preparation of a wider variety of pyrrolidinones **251** and allow for further functionalisation (Scheme 83).

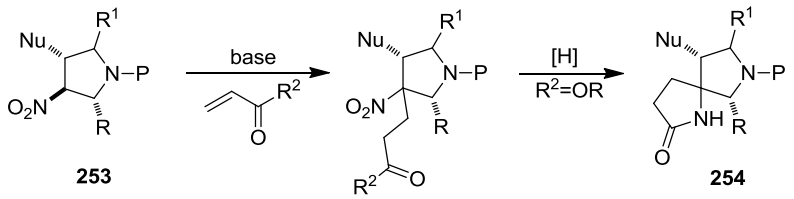
Moreover, some further modifications of the pyrrolidinone core could be attempted. For example, a possible reaction with a Grignard reagent at the amide carbonyl could give **252**, which after an ionic reduction with $Et_3SiH/BF_3.OEt_2$ could give the alkylated product **253** (Scheme 83).[118]



Scheme 83. Synthesis and possible functionalisations of pyrrolidinones **251**

Compounds **253** still contain an acidic proton alpha to the nitro group that would give a reacting nitronate anion by deprotonation. This could then be reacted with electrophiles such as acrylates (Michael addition). Subsequent reduction of the nitro

group could lead to ring closure and yield interesting spiro fused heterocycles **254** (Scheme 84).



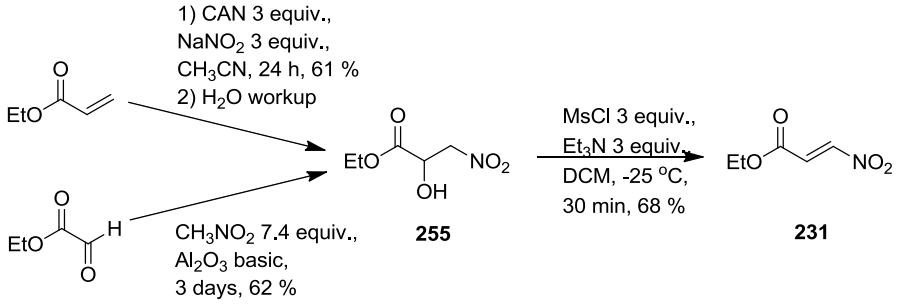
Scheme 84. Reaction of pyrrolidinones **253** with acrylates

Those are just a few of the possible transformations that could be studied and give rise to interesting heterocyclic structures. With the possible control of the absolute stereochemistry in the initial conjugate addition step, these structures could be made in enantiomerically pure form. The success of this methodology would be confirmed by the synthesis of one or more natural products.

2.3 Stereoselective synthesis of pyrrolidinones *via* Nitro-Mannich reaction

2.3.1 Synthesis of starting materials

With the methodology for the synthesis of pyrrolidinones already developed, we set out to expand the scope of this tandem synthesis. This required access to the non-commercially available starting material ethyl 3-nitroacrylate **231**. An efficient synthesis of this material was required as a considerable quantity of it was needed for the study. Two possible routes to **231** have been used before[119] (Scheme 85). In the first route, reaction of ethyl acrylate with ceric ammonium nitrate (CAN) and sodium nitrite gave nitroalcohol **255**,[120] which upon treatment with mesyl chloride and triethylamine gave the desired nitroacrylate **231** in 41 % yield overall. In the second route, the same nitroalcohol could be obtained by reaction of ethyl glyoxylate with nitromethane in the presence of alumina,[121] giving a total yield of 42 % for **231**.



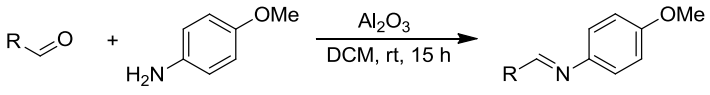
Scheme 85. Synthesis of nitroacrylate **231**

In this thesis, repeating the synthesis of nitroalcohol **255** from ethyl acrylate was attempted many times and it was found that the yield of the product was variable (32-45%) depending on the source of CAN used. It was found that using freshly dried and ground CAN gave a better yield 59-63%.

The synthesis of **255** from ethyl glyoxylate however, was more challenging. Use of neutral alumina, as in the literature procedure,[120] gave a very low yield, whereas use of basic alumina and extension of the reaction time to 3 days gave a 62% yield of the nitroalcohol (Scheme 85). It was thought that a catalytic amount of base would also catalyse the reaction and indeed 10 mol % of Et_3N gave 56% yield, while reducing the base to 2.00 mol % gave 44% yield after 24 h. The reaction of glyoxylate with basic alumina was our preferred method for the synthesis of nitroalcohol **255**, as it required less quantities of reagents (ethyl acrylate method required 3 equiv. of CAN and $NaNO_2$). Furthermore, it was much cleaner and easier to purify, as the starting materials were volatile, thus could be removed *in vacuo*, thereby avoiding chromatography. Subsequent dehydration by mesylation proceeded smoothly to give the desired nitroacrylate in 42% overall yield.

The final required reagents were the PMP protected imines, both heterocyclic and alkyl. The heterocyclic imines were synthesised *via* the condensation of the corresponding aldehyde with *para*-anisidine in a 1:1 ratio, in the presence of a dehydrating agent, usually basic Al_2O_3. The reaction was performed in DCM at room temperature and was usually completed within 15 h. The products were usually isolated as solids that were stable at -20 ^oC. The products were used without further purification when ^1H NMR showed a purity of >95% and recrystalised otherwise (Table 1).

Table 1. Synthesis of heterocyclic imines



Entry	Imine	R	Yield (%)
1	**256**	2-pyridyl	91
2	**257**	3-pyridyl	93

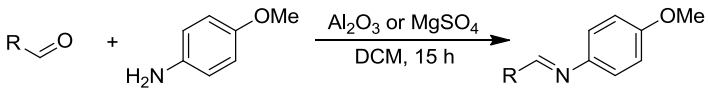
3	**258**	3-indolyl	95
4	**259**	3-*N*-methylindolyl	93[a]
5	**260**	3-*N*-tosylindolyl	89
6	**261**	2-pyrrolyl	68[b]
7	**262**	2-*N*-methylpyrrolyl	64[b]
8	**263**	2-*N*-tosylpyrrolyl	97
9	**264**	2-thiazolyl	92
10	**265**	2-oxazolyl	93

[a]Synthesised from imine **258** by methylation.

[b]After recrystallisation, provided by colleague Paul Koovits.[122]

The synthesis of alkyl imines was more difficult than that of the heterocyclic ones because of their instability. Alkyl imines **267** and **268** required $MgSO_4$ as the dehydrating agent. With imine **266** the reaction should be performed at -78 ^oC and the imine was only stable for a few days at -5 ^oC (Table 2). This instability can be attributed to the tautomerisation of the imine to an enamine that could undergo side reactions.

Table 2. Synthesis of alkyl imines



Entry	Imine	Method	R	Yield (%)
1	**266**	Al_2O_3/rt	Methyl	-
2	**266**	Al_2O_3/-78 ^oC	Methyl	97
3	**267**	$MgSO_4$/rt	2,2-dimethoxyethyl	97
4	**268**	$MgSO_4$/rt	Cinnamyl	98

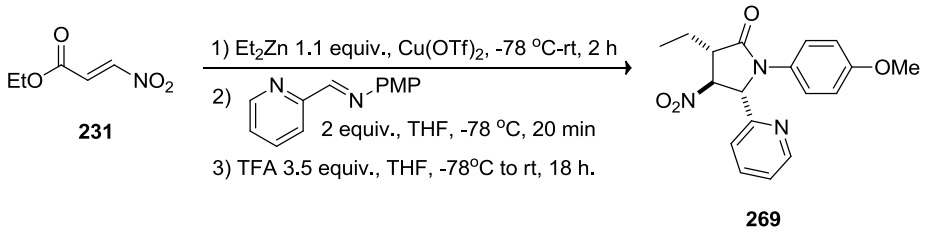
2.3.2 Expansion of the reaction scope

With ethyl 3-nitroacrylate **231** in hand, we continued towards the synthesis of pyrrolidinones using the conjugate addition/nitro-Mannich reaction. Using the

previously developed methodology,[119] an expansion of the scope of the reaction, was attempted, in particular to the use of nitrogen containing heterocyclic imines and some alkyl imines.

The study of the reaction of *N*-containing imines started from imine **256** (Table 1). Reaction of this imine under the developed conditions gave the product pyrrolidinone **269** in 50% yield. As this yield was rather low, optimisation of the reaction was attempted. A number of modifications to the reaction conditions were attempted, such as altering the solvent, the equivalents of acid, the reaction time, the temperature and the protecting group (Table 3), however none of these led to any significant increase of the yield of **269**.

Table 3. Optimisation of the synthesis of pyrrolidinone **269**

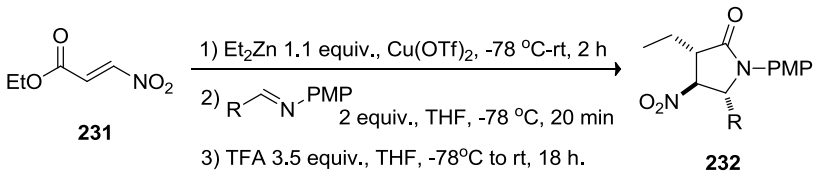


Entry	Reaction conditions	Yield of 269
1	As shown	50%
2	5.5 equiv. of TFA used	24%
3	Ether used as solvent, 48 h reaction time	32%
4	DCM used as solvent (steps 2 and 3)	32%
5	Step 3 left for 48 h	54%
6	Step 3: 5 Å molecular sieves added	21%
7	Step 3 left for 15 h at rt then 5 h reflux	45%
8	Triflic acid used instead of TFA	20%
9	Lewis acid $Ti(O^iPr)_4$ (3 equiv.) instead of TFA	15%
10	OMP imine used instead of PMP	No product

The general reaction conditions shown above were then used in the synthesis of other heterocyclic pyrrolidinone analogues (Table 4). Imines **256**, **257**, **264** and **265** gave average yields (42-58 %) of pyrrolidinones **232** as single diastereoisomers, whereas the indole and pyrrole imines **258** and **261** gave no product. The failure of this reaction may be due to either the electron donating character of the pyrrole and indole rings or by possible side reactions that lead to degradation.

In light of this result, the reaction of both the *N*-methyl and the *N*-tosyl protected imines of pyrrole and indole was attempted. Not surprisingly, the *N*-Me protected imines **259** and **262** gave no product (by ^{1}H NMR), while the *N*-tosyl protected ones gave a successful reaction. This result confirmed the previous hypothesis, as the presence of the Tosyl group removes electron density from the two heterocycles making imines **260** and **263** more electrophilic. In the case of imine **260**, a 56% yield of pyrrolidinone **271** was isolated, while imine **263** gave only a poor yield of 33% of **272**, isolated as a mixture of diastereomers (*dr* 85:15).

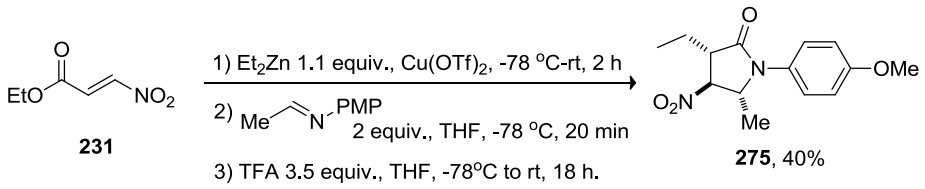
Table 4. Synthesis of heterocyclic substituted pyrrolidinones **232**



Entry	Product	R group	Yield
1	**269**	2-pyridyl	50%
2	**270**	3-pyridyl	42%
3	-	3-indolyl	No product
4	-	3-*N*-methylindolyl	No product
5	**271**	3-*N*-tosylindolyl	56%
6	-	2-pyrrolyl	No product
7	-	2-*N*-methylpyrrolyl	No product
8	**272**	2-*N*-tosylpyrrolyl	33%
9	**273**	2-thiazolyl	58%
10	**274**	2-oxazolyl	53%

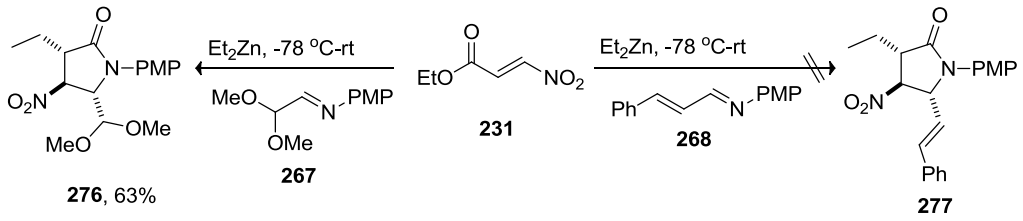
The use of alkyl imines for the synthesis of pyrrolidinones has been investigated before.[116] It was found that secondary imines like isopropyl and cyclohexyl gave pyrrolidinones **235** and **236** in medium yield, while tertiary and primary imines were less successful (Figure 10, section 2.1). The reason for this poor result is postulated to be the instability of primary imines due to their tautomerisation to enamines.

For the same reason, when the reaction of imine **266** derived from acetaldehyde (section 2.3.1) was performed, only a complex mixture of products was observed. However, when imine **266** was synthesised at -78°C and used straight after without warming, pyrrolidinone **275** could be isolated in 40% yield as a single diastereoisomer (Scheme 86).



Scheme 86. Synthesis of pyrrolidinone **275**

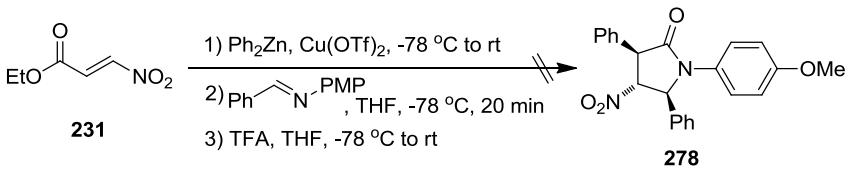
The usefulness of the developed methodology would be considerably increased if the group at the rings C^5 position provided room for further functionalisation, as that would allow the synthesis of more complicated structures. One useful group to have at this position would be a formyl group. A possible alternative to installing a formyl group could be to have a masked aldehyde that would later be deprotected. Indeed, reaction of acetal-imine **267** was successful and yielded pyrrolidinone **276** in 63% yield (Scheme 87). Another useful functionality to have at the C^5 position would be an alkene substituent, such as the one seen in compound **277**. The presence of a double bond offers many derivatisation options, as an alkene could be transformed to a variety of other functional groups. However, from the reaction of cinnamaldehyde-derived imine **268** no pyrrolidinone could be isolated, as the crude reaction mixture contained only the 1,4-addition product of Et_2Zn to **231** and degradation products.



Scheme 87. Attempts to synthesise pyrrolidinones **276** and **277**

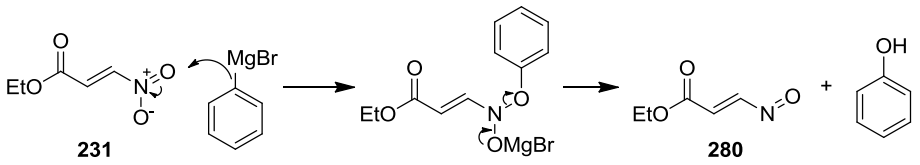
2.3.3 Use of other dialkylzinc reagents

In light of the success of diethylzinc, the use of other dialkylzinc reagents as nucleophiles for this 1,4-addition/nitro-Mannich reaction was then investigated. Dimethylzinc has already been shown to be as good a nucleophile as diethylzinc, however the use of diphenylzinc for the synthesis of pyrrolidinones was unsuccessful.[119] As such, it was decided to reinvestigate the use of diphenylzinc. The 1,4-addition reaction of diphenylzinc to nitroacrylate **231** was found to be very slow. Increasing the equivalents of Ph_2Zn to two or increasing the reaction time for this step to 4 days did not result in any improvement. Also, increasing the reaction time of the nitro-Mannich/lactamisation part of the reaction or using the stronger triflic acid instead of TFA was also not beneficial as the reaction gave a complicated mixture of products and none of the desired pyrrolidinone **278** (Scheme 88).



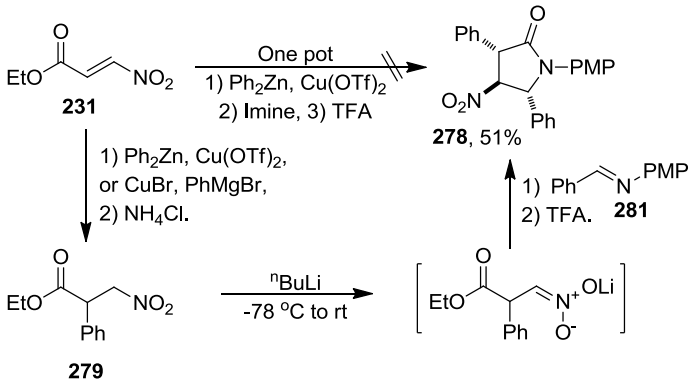
Scheme 88. Attempt to synthesise pyrrolidinone **278**

In light of these results, it was decided to investigate doing the reaction stepwise and isolating the intermediate 1,4-addition product **279**. It was therefore necessary to look at other ways of conducting the initial 1,4-addition reaction. The reaction of nitroacrylate **231** with diphenylzinc (1.1 equiv.) in the presence of $Cu(OTf)_2$ (5 mol %) gave nitroalkane **279** in 60% yield. The 1,4-addition of the phenyl group was also attempted, where 1 equiv. of $CuBr{\cdot}SMe_2$ was premixed with PhMgBr at -40 °C and then reacted with the nitroalkene, giving 48% yield of **279**.[123] When the reaction of nitroacrylate **231** with PhMgBr was attempted at -78 °C, no 1,4-addition product was isolated but phenol was unexpectedly observed in the crude reaction mixture. This could be explained by the addition of the Grignard reagent to the nitro group, followed by elimination of phenol to form nitrosoalkene **280** (Scheme 89). This kind of reactivity has been reported in the first step of the mechanism of Bartoli's indole synthesis.[124]



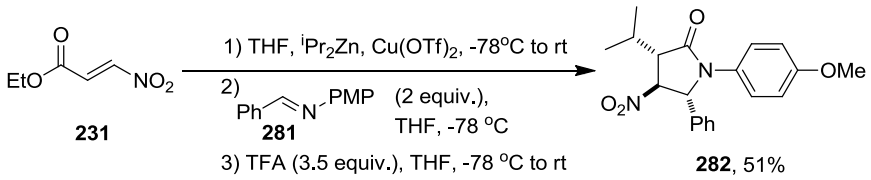
Scheme 89. Proposed mechanism for phenol formation

Subsequently, deprotonation of nitroalkane **279** with ^{n}BuLi, followed by nitro-Mannich reaction with imine **281** and lactamisation, gave **278** in 51% yield (Scheme 90).



Scheme 90. Two-step synthesis of pyrrolidinone **278**

The use of an alternative dialkylzinc reagent, diisopropylzinc, was also investigated. The zinc reagent was synthesised from $ZnBr_2$ and ^{i}PrMgCl, purified by distillation and used as a solution in hexane, after titration with I_2/LiCl.[125,126] Using imine **281**, the reaction worked well to give the expected pyrrolidinone **282** in 51% yield (Scheme 91).



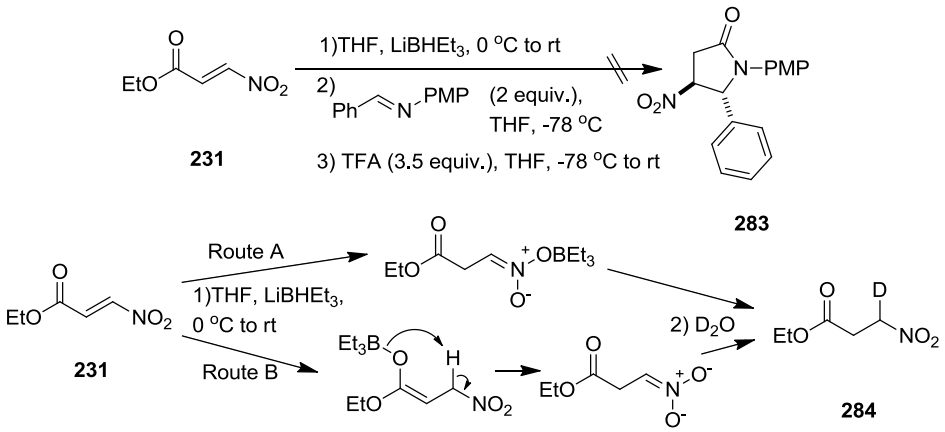
Scheme 91. Use of diisopropylzinc in the synthesis of **282**

2.3.4 Superhydride® as a nucleophile

The 1,4-addition of Superhydride® to nitroalkenes and subsequent nitro-Mannich reaction has been reported.[36] Use of a hydride nucleophile to make pyrrolidinones would be useful, as the expected product **283** would be unsubstituted in the C^3 position which opens up new possibilities for derivatisation, like for example enolate

alkylation (Scheme 92). Indeed the Superhydride® added to the nitroalkene in the predicted way, however no cyclisation product was observed. Heat should potentially energetically help the lactamisation to occur, though when the reaction was refluxed in THF after the nitro-Mannich reaction, only degradation products were isolated.

In all our investigations of 1,4-additions to nitroacrylate **231** (section 2.5.2), nucleophilic additions occurred 1,4 to the nitroalkene and not 1,4 to the acrylate. It was however desired to confirm that the hydride nucleophile adds 1,4 to the nitroalkene, so a deuteration experiment was performed. After 1,4-addition of Superhydride®, the mixture was quenched with AcOD, followed by aqueous workup. Indeed some deuteration (40%) was observed α to the nitro group (nitroester **284**, Scheme 92) and no deuteration α to the ester group. It is possible though that the hydride added 1,4 to the acrylate and then a tautomerisation occurred that would give a nitronate (Route B), which on deuteration would give the same product **284** (Scheme 92). Therefore this experiment remains ambiguous, however we believe that this is not the reason of the failure to obtain pyrrolidinone **283**. The percentage of deuteration was determined from the integration of the ^{1}H NMR spectrum of the crude product.



Scheme 92. Attempt to synthesise pyrrolidinone **283**

From ^{1}H NMR analysis of the crude reaction mixture it can be seen that the nitro-Mannich reaction is indeed occurring, but the initially formed β-nitroamine **285** does not cyclise. Based on the previous work on hydride conjugate addition/nitro-Mannich reactions (Scheme 77, section 2.1), it was assumed that the major product was *anti*-**285** (Figure 11).[36] It is surprising that cyclisation of β-nitroamine **285** does not occur even after heating, which could be explained by the rate of degradation of **285** by

retro-addition being faster than the rate of cyclisation. Heating (70 °C) has been used before to afford the cyclisation of similar β-nitroamines by Dixon and co-workers, who reported the synthesis of densely substituted pyrrolidinones **226** from nitroester **224** (Scheme 76, section 1.5).[11]

Compound **285**, as well as diethylzinc adduct **286** (intermediate to pyrrolidinones **232**), would react in the reactive conformations A and B, respectively. It is clear that conformation B has more steric hindrance around the ring because of the presence of the ethyl substituent. The Thorpe-Ingold effect states that increasing the substitution on a tetrahedral centre leads to enhancement of the intramolecular reactivity between parts of the remaining two substituents.[127] Thereby, it is expected that conformation A of the less substituted nitroamine **285** would cyclise slower than conformation B of the more substituted **286**.

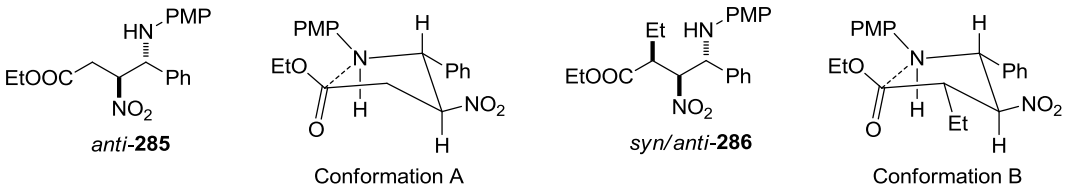


Figure 11

2.3.5 Tandem reaction

A simplification to the tandem reaction would be to have the imine and nitroalkene in the same solution and add to this mixture diethylzinc, followed by TFA. In this reaction, it is desired for Et_2Zn to react preferentially with the nitroalkene and not the imine, something that is expected due to the more electrophilic nature of the nitroalkene. This tandem reaction was attempted for the synthesis of the parent pyrrolidinone **233**. In this reaction, a solution of nitroalkene **231**, imine **281** (2 equiv.) and $Cu(OTf)_2$ (5 mol %) in THF was cooled to -78 °C and Et_2Zn (1.1 equiv.) was added. After 10 min, the reaction was warmed to room temperature and when the nitroalkene was consumed (by TLC), TFA was added as usual and the same reaction conditions and workup were carried out according to the general procedure. The reaction gave the product **233** in 52% yield, as opposed to the originally obtained 67% yield with the one-pot sequential addition.

2.3.6 Relative stereochemistry

As previously described, the pyrrolidinones synthesised by the 1,4-addition/nitro-Mannich/lactamisation methodology described above were isolated mostly as single diastereoisomers, with the exception of pyrrolidinone **272** (85:15 *dr*). Previous work showed the relative stereochemistry of the pyrrolidinones in this reaction to be *anti*/*anti* in the ring structure of **269**, using a combination of X-ray crystallography and ^{1}H NMR coupling constant data.[119] The same stereochemistry also appeared in our work by the crystal structure of pyrrolidinone **269** (Figure 12) and later by that of trifluoroacetamide **287** derived from pyrrolidinone **241** (section 2.3.8).

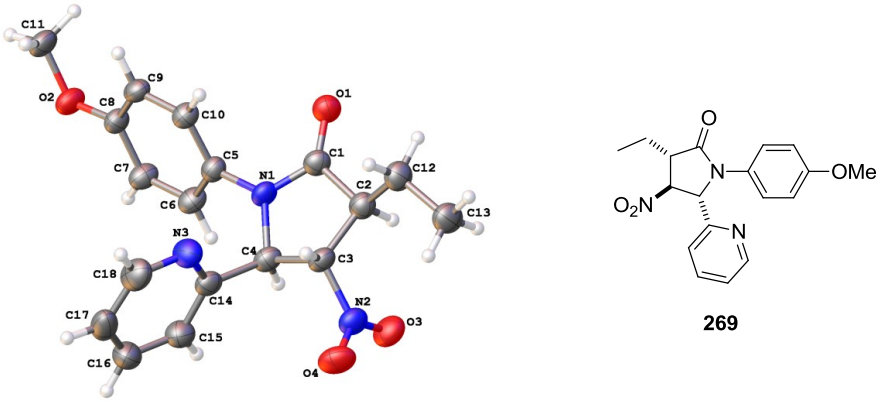


Figure 12. X-ray crystal structure of (±)-**269**

As it was not possible to obtain X-ray crystal structures of all the analogues synthesised, the relative stereochemistry of the rest of the pyrrolidinones was assigned by comparison of their ^{1}H NMR coupling constants. In the 5-membered ring of **288** with a *trans*/*trans* relative stereochemistry it is expected that all substituents are in *pseudo*-equatorial positions (Figure 13). In previous work, couplings of 5.3-7.5 Hz were reported for J_{HaHb} (Figure 13) and 4.2-5.9 Hz for J_{HbHc}.[119] In our analogues, couplings J_{HaHb} were found to be in the range of 4.6-8.0 Hz and couplings J_{HbHc} in the range of 3.4-6.3 Hz. Based on these results, it was assumed that the relative stereochemistry observed in the X-ray crystallographic data is also present in other analogues. A full table of coupling constants is presented in appendix 1.

Pyrrolidinone **272** is an exception as it was isolated as a mixture of two diastereoisomers, the major diastereoisomer having a J_{HaHb} of 2.4 Hz and a J_{HbHc} of 1.6 Hz as opposed to a J_{HaHb} of 7.4 Hz and a very small J_{HbHc} (≈ 0 Hz) for the minor diastereoisomer. In NOE studies of the major diastereoisomer, irradiation of the

C*H*NO_2 peak at δ 4.94 ppm caused a 1.1% and 1.0% enhancement for the protons C*H*N and C*H*CH_2, respectively (Figure 13). Irradiation of the C*H*NO_2 peak of the minor diastereoisomer at δ 5.33 ppm caused a 1.8% and 3.1% enhancement for the protons C*H*N and C*H*CH_2, respectively (Figure 13). The larger enhancement between the protons C*H*CH_2 and C*H*NO_2 indicates that those protons are closer in space in **272b** than in **272a**. Consequently, the major diastereoisomer is **272a** bearing a *trans/trans* relative stereochemistry and the minor one *cis/trans*-**272b**. Furthermore, molecular modelling of these two structures using PCMODEL software,[128] predicts for the *trans*/*trans* diastereoisomer the J_{HaHb} and J_{HbHc} values being 0.7 and 0.8 Hz respectively and for the *cis*/*trans*, 6.3 and 0.9 Hz. These values broadly agree with our experimental data. Deviation of up to 1.0 Hz in the calculated couplings constants is expected based on the error limit of the calculation. Moreover, contribution of other conformations to the experimental coupling constants, in particular the ring flipped conformation would also shift the observed value from the calculated one that corresponds to the lowest energy conformation only.

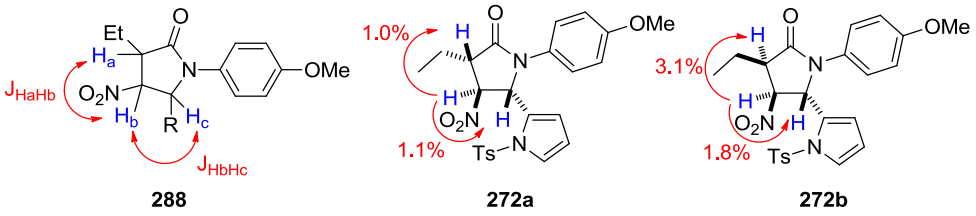
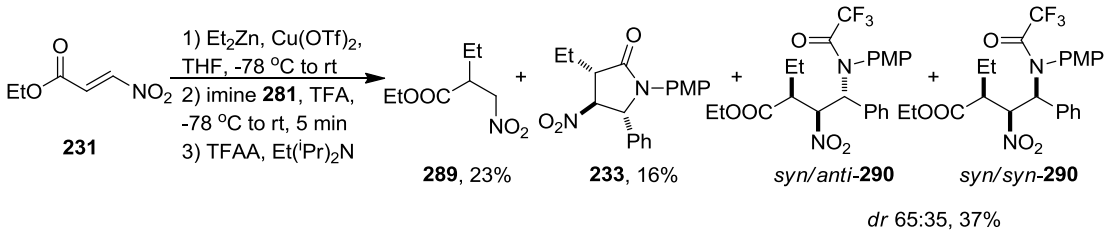


Figure 13

2.3.7 Origin of diastereoselectivity

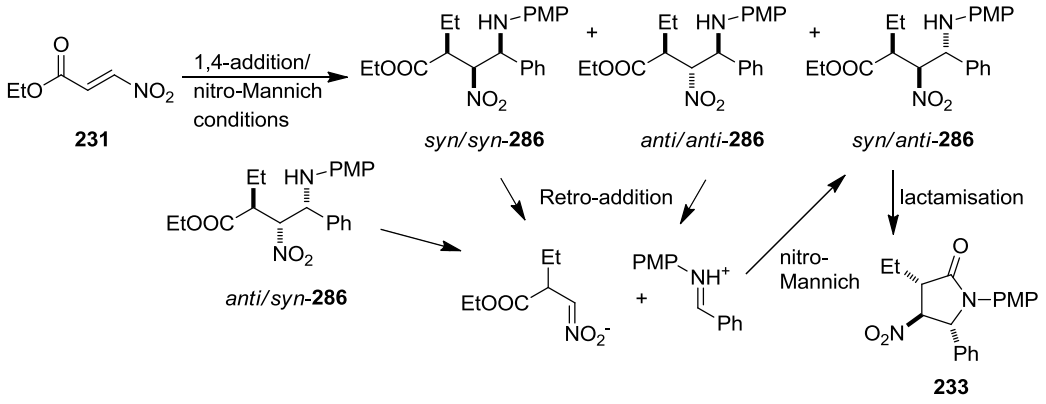
Previous work on the 1,4-addition of dialkylzinc reagents to nitroalkenes followed by a nitro-Mannich reaction has shown the *syn*/*anti* *β*-nitroamine to be the major product in homogenous solutions (section 2.1).[35] Initial results of the reaction with nitroacrylate **231**, where the reaction was quenched with aqueous $NaHCO_3$ after 5 min at rt and any uncyclised *β*-nitroamines were protected as trifluoroacetamides, showed that 4 products were isolated (Scheme 93). Those were the 1,4-addition product **289**, pyrrolidinone **233** and the two trifluoroacetamides *syn*/*anti*-**290** and *syn*/*syn*-**290**, with the *syn*/*anti* diastereoisomer being the major one.[116] The two trifluoroacetamides were formed from TFA-protection of *β*-nitroamines *syn*/*anti*-**286** and *syn*/*syn*-**286**. It was assumed that **289** originates from degradation of other *β*-nitroamine diastereoisomers of **286**, as was previously observed during

trifluoroacetamide protection of other *β*-nitroamines of this type.[35] The stereochemistry of **233** corresponds to the cyclisation of the major *β*-nitroamine diastereoisomer *syn*/*anti*-**286**.



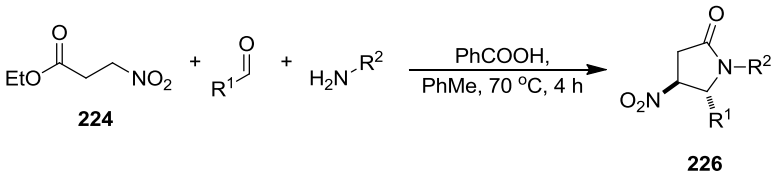
Scheme 93. Initial studies of the nitro-Mannich reaction of nitroacrylate **231**[114]

Also in previous studies, the synthesis of **233** was repeated in d^8-THF and analysed by ^{1}H NMR in regular time intervals after warming the reaction mixture to ambient temperature.[116] Initially only the *syn/anti*-**286** and pyrrolidinone **233** were observed, with traces of other *β*-nitroamine diastereoisomers. The ratio of *syn/anti*-**286** to **233** gradually decreased with time, suggesting that lactamisation is the slowest step in this sequence. It is known that the *syn/anti*-**286** diastereoisomer is the kinetic product in conjugate additions of diethylzinc to nitroalkenes and subsequent nitro-Mannich reaction.[35] It is also known that *β*-nitroamines are susceptible to retro- and re-addition.[35] As any other isomers of pyrrolidinones **288** were rarely observed, it could be postulated that only *syn/anti*-**286** cyclises to give the all equatorial product **233**, presumably irreversibly. The transition state to the all equatorial product must be lower in energy than the transition state to other diastereoisomers. Other *β*-nitroamine diastereoisomers like the *anti/anti* and *syn/syn* have been isolated before in similar nitro-Mannich reactions, while an *anti/syn* *β*-nitroamine was observed by ^{1}H NMR but never isolated.[114] These diastereoisomers have to equilibrate to *syn*/*anti*-**286** before cyclisation (Scheme 94).



Scheme 94. Mechanism for the formation of **233** as a single diastereoisomer

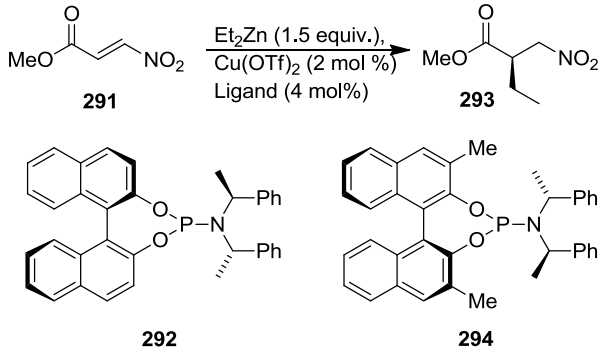
This scenario is also supported by the results of Dixon and co-workers who reported the synthesis of densely substituted pyrrolidinones **226** from nitroester **224** (Scheme 95).[11] In this work the authors suggested, based on some kinetic data, that the lactamisation step is also the rate determining in this related cascade reaction. However, a minor diastereoisomer of pyrrolidinones **226** is observed in many cases, something that is not surprising due to the harsher conditions (70 ^{o}C in toluene). The authors suggest that the origin of stereocontrol lies in the selective lactamisation of the diastereoisomer bearing all the substituents in *pseudo*-equatorial positions and not in the nitro-Mannich reaction which was reversible.



Scheme 95. Dixons' synthesis of pyrrolidinones **226**[11]

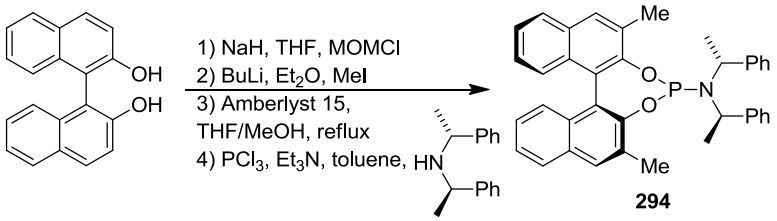
2.3.8 Asymmetric methodology

The asymmetric 1,4-addition of diorganozinc reagents to nitroalkenes has been reported.[50,51,129] In particular, the 1,4-addition of diethyl zinc to nitroalkene **291** has been reported to give up to 92% *ee* using a copper complex with a BINOL-based enantiopure phosphoramidite ligand as the catalyst.[130] According to the authors, use of ligand **292** gave 1,4-addition product **293** of 77% *ee* while ligand **294** gave 92% (Scheme 96). Other ligands such as **69** have been used in asymmetric 1,4-addition reactions to other nitroalkenes (Scheme 33, section 1.2.2) and were also applied successfully in conjugate addition/nitro-Mannich reactions.[35] However, we concentrated on phosphoramidite ligands as those were shown to be effective with nitroacrylates.



Scheme 96. The asymmetric conjugate addition of diethylzinc to nitroacrylate **291**

The asymmetric conjugate addition using ligand **292** and nitroacrylate **231**, followed by a subsequent nitro-Mannich/cyclisation reaction with the imine **281**, has been reported.[119] This reaction gave the enantioenriched pyrrolidinone **233** in 52% *ee*. In order to improve this result, the synthesis of ligand **294** and subsequent use as a catalyst for this reaction, was pursued. The synthesis was a 4 step procedure, starting from racemic BINOL (Scheme 97).[130,131] In the last step of the synthesis, the authors separated the two diastereomers of the catalyst using chromatography. However, in our hands even after two chromatographic separations, it was only possible to obtain a sample of ligand **294** with 94% *de*. Use of this ligand in the asymmetric conjugate addition on nitroacrylate **231** and subsequent nitro-Mannich reaction with imine **281** gave pyrrolidinone **233** in 73% *ee* and 67% yield. In light of this result, the synthesis of pure ligand **294** was carried out, starting from (*S*)-BINOL instead of racemic BINOL. The diastereomerically pure ligand indeed gave an improved *ee* of 79% and a yield of 72%. During the HPLC resolution of pyrrolidinone **233**, it was also observed that partial crystallisation from a solution of **233** in ^{i}PrOH led to an improved *ee* in the mother liquors. This indicates that the racemate of **233** is more crystalline than either of the single enantiomers, something that is common.[132] As such, a recrystallisation of the product from ^{i}PrOH gave racemic crystals (18% by mass) and a remainder solution of 99% *ee*. Impressively, this meant that the enantiomerically pure pyrrolidinone **233** could now be isolated in 59% yield overall and 99% *ee*.

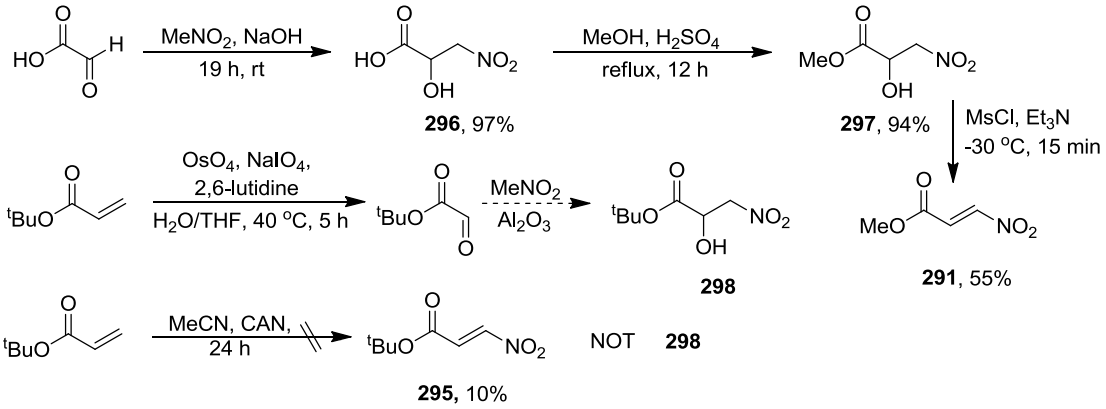


Scheme 97. Synthesis of phosphoramidite ligand **294**

We were puzzled with the fact that a lower *ee* of pyrrolidinone **233** was obtained from our reaction than the one obtained by Sewald and co-workers for the 1,4-addition step. In particular, with ligand **292** the 1,4-addition step gave 77% *ee* of **293** according to the literature,[130] but only 52% *ee* was obtained in our product **233**.[119] Similarly with ligand **294**, from a reported 92% *ee* of **293** in the 1,4-addition step, only 79% *ee* of **233** was obtained in our one-pot reaction. It was postulated that this loss of enantioselectivity might be caused by the choice of nitroacrylate. Specifically we had been using the ethyl ester **231**, whereas the literature work used the methyl

ester **291**. It was assumed that the ethyl group is too far from the reaction centre to make a difference. Another possible reason could be that some degree of epimerisation at the C^3 position of the final product **233** could be occurring under the acidic reaction conditions. To test the second hypothesis, an experiment was carried out, where a sample of pyrrolidinone **233** of 79% *ee* was subjected to the reaction conditions, in particular the presence of TFA overnight. However, no loss of enantioselectivity was observed, indicating that this was not the reason of the reduced *ee*.

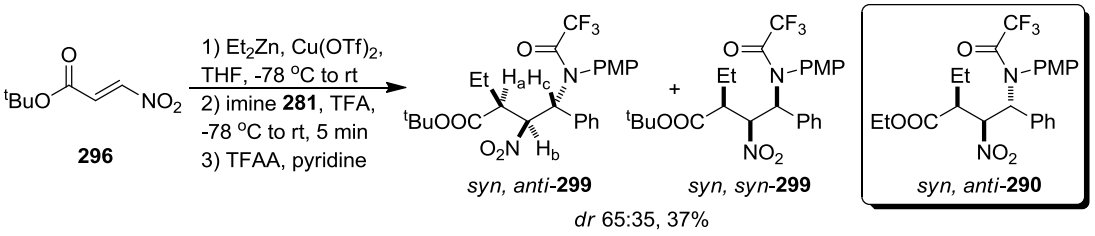
To test the first hypothesis it was decided to synthesise two new nitroacrylates, **291** and **295** bearing a small and a large alkoxy-group, respectively (Scheme 98). Nitroacrylate **291** was made in a 3 step synthesis from glyoxylic acid. A condensation of glyoxylic acid with nitromethane gave 2-hydroxy-3-nitropropionic acid **296**,[133] followed by esterification with methanol to nitroalcohol **297**[134] and dehydration to the desired nitroalkene **291**,[135] in a total yield of 50%. The synthesis of nitroacrylate **295** though was more challenging. Initially, a reported method was attempted to make nitroalcohol **298** starting from ^{t}butyl acrylate.[136] However, this procedure in our hands, didn't yield any of the desired product, probably because of the potential poor quality of reagent OsO_4 used (Scheme 98). In light of this, a different route to the nitroalkene **295** was then investigated, using the same procedure used before for the synthesis of nitroalkene **231**.[120] Surprisingly, when the reaction of ^{t}butyl acrylate with CAN and $NaNO_2$ was performed, no nitroalcohol **298** was observed in NMR. Instead the final nitroalkene **295** was detected, which was isolated in poor yield (10%).



Scheme 98. Synthesis of nitroacrylates **291** and **295**

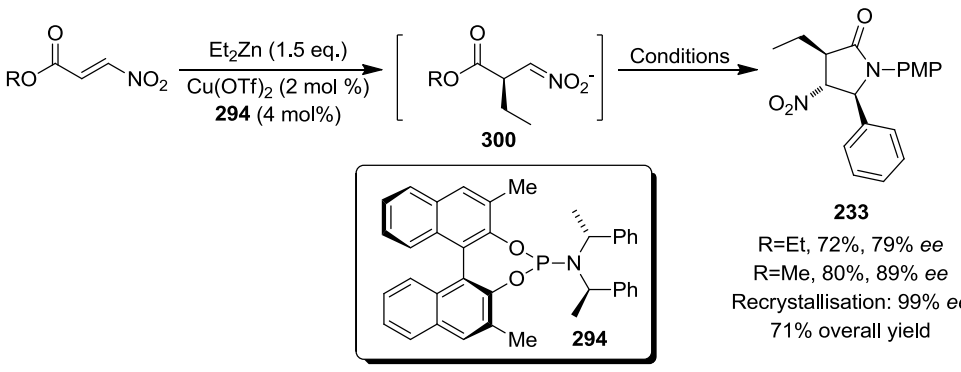
After the synthesis of the two new nitroalkenes, the one pot 1,4-addition/nitro-Mannich/lactamisation reactions with diethylzinc were attempted. As expected,

nitroalkene **291** reacted in a similar way to the ethyl ester **231** to give pyrrolidinone **233** in 66% yield. The reaction of nitroalkene **295** however was different; even though the 1,4-addition of diethylzinc occurred normally and some nitro-Mannich products were observed on ^{1}H NMR, lactamisation did not occur and no pyrrolidinone **233** was isolated. Instead, only the uncyclised nitro-Mannich product was obtained. Heating the reaction mixture to reflux only led to degradation. In a separate experiment, the uncyclised nitro-Mannich products were isolated after protection as trifluoroacetamides **299** in 26% yield as a mixture of two diastereoisomers in 65:35 *dr* (Scheme 99). The major diastereoisomer had a J_{HaHb} value of 4.0 Hz and a J_{HbHc} of 10.2 Hz, whereas the minor one had J_{HaHb} value of 2.2 Hz and a J_{HbHc} of 11.6 Hz. Comparison with the coupling constants previously reported for trifluoroacetamide **290** (J_{HaHb} = 3.6 Hz, J_{HbHc} = 10.6 Hz)[114] showed that they were in agreement with the values of our major diastereoisomer. We can therefore tentatively conclude that our major diastereoisomer is *syn/anti*-**299** and our minor one is *syn/syn*-**299** (Scheme 99).



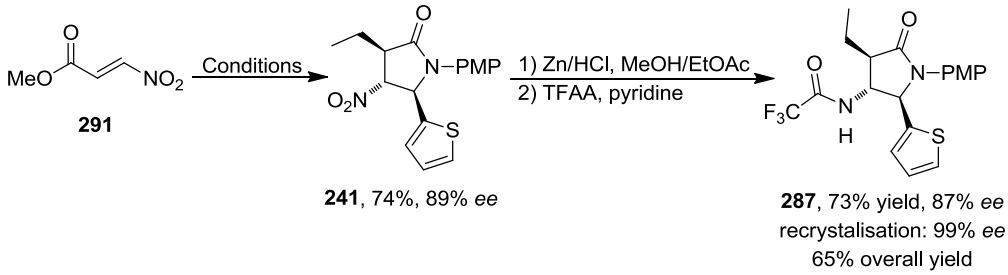
Scheme 99. Nitro-Mannich reaction of nitroacrylate **296**

An asymmetric reaction of nitroalkene **291** was attempted using the same ligand **294** as before. The reaction was indeed better than that of nitroalkene **231**, giving 89% *ee* and 80% yield. This is very close to the reported value of 92% *ee* for the asymmetric 1,4-addition of diethylzinc on the same substrate (Scheme 100).



Scheme 100. Asymmetric synthesis of **233**

Lack of knowledge of the absolute stereochemistry of the 1,4-addition, prompted us to seek proof of the stereochemistry using X-ray crystallography. In order to accomplish this, it was necessary to synthesise pyrrolidinone **241** containing the heavy atom sulfur, in an asymmetric manner. Indeed, the desired pyrrolidinone was made in 89% *ee*, suggesting that the enantioselectivity remains independent of the imine used in the reaction. However, no suitable crystals could be obtained from **241**. It was thought that the conversion of this pyrrolidinone to trifluoroacetamide **287**, *via* reduction of the nitro functionality and TFA-protection, would make the compound more crystalline. This was achieved in good yields and without significant loss of *ee* and the final product could be recrystallised to 99% *ee* (Scheme 101).



Scheme 101. Asymmetric synthesis of **241** and conversion to trifluoroacetamide **287**

Fortunately it was possible to obtain a crystal structure of trifluoroacetamide **287** and to determine its absolute stereochemistry (Figure 14), which was found to be (*R,R,R*). This requires that the asymmetric 1,4-addition step gives nitronate **300** with the chiral centre in the *R* configuration.

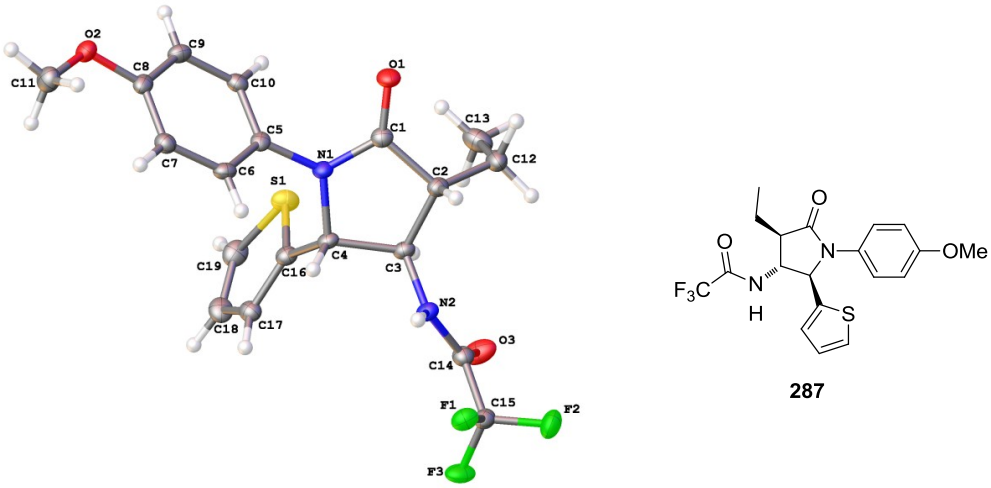


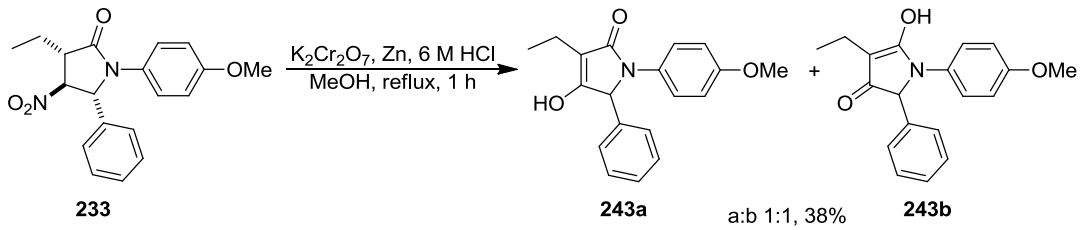
Figure 14. X-ray crystal structure of **287**

2.3.9 Further functionalisation of the parent pyrrolidinone

2.3.9.1 Nef reaction

One of the targets of this project was to perform some functional group interconversions on the pyrrolidinone structure **233**, something that will illustrate its usefulness as a synthetic scaffold.

One reaction that proved to be problematic in previous studies is the Nef reaction.[119] Various methods of performing the Nef reaction exist in the literature, including the typical base/acid reaction,[137] reductive methods,[76] oxidative methods[138,139] and others[140] (section 1.3.2). The reaction that was performed previously in our system used $CrCl_2$ and gave a poor yield of the product **243a** and its tautomer **243b** (Scheme 102).[140]

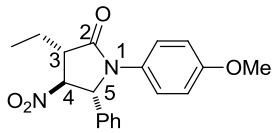


Scheme 102. The Nef reaction of **233**

Many other methods were attempted in order to improve this result, but were unsuccessful. Treatment of pyrrolidinone **233** with a phosphate buffer at pH=13 in $MeOH/H_2O$ and oxone (1.00 equiv.), followed by a quench of aqueous 3 M HCl, gave decomposition.[138] A similar result was obtained by a biphasic reaction with aqueous NaOH, DCM and $Bu_4N^+HSO_4^-$ followed by addition of $NaClO_2$ (1.50 equiv.),[139] as well as reaction with CAN (1.00 equiv.) and Et_3N (7.00 equiv.) in $MeCN/H_2O$ at 60 ^oC.[141] Reaction with $NaHCO_3$ in DCM/H_2O/dioxane at 70^oC,[142] gave recovery of the starting material, as did reaction with DIPEA (2.00 equiv.) followed by H_2SO_4 (10.0 equiv.). The same result was also obtained by reaction with LDA (1.05 equiv.), followed by H_2SO_4 (10.0 equiv.) and reaction with DBU (5.00 equiv.) in MeCN at 60 ^oC,[143] even though the later was reported to work well with secondary nitroalkenes. Simple treatment with NaOH (2.00 equiv.) in THF/H_2O followed by H_2SO_4 (10.0 equiv.) gave decomposition, while by using HCl 2 M (5.00 equiv.) instead, some starting material was also recovered. Reaction with ^tBuONa (1.50 equiv.) led to decomposition. Treatment with Lewis acids such as $SnCl_4$ (2.00 equiv.) in DCM and

$TiCl_4$ (4.00 equiv.) at rt, followed by aqueous workup, led to recovery of the starting material. Reaction with $NaNO_2$ (15.0 equiv.) and AcOH (50.0 equiv.) in DMSO at room temperature,[144] gave decomposition as did reaction with $TiCl_3$ (4.00 equiv.) in THF.[76] When the $TiCl_3$ reaction was attempted in the presence of a buffered solution at pH=5, only recovered starting material was isolated.

Previous studies of the alkylations of pyrrolidinone **233** have shown an unexpected reactivity with bases.[119] Therefore, it was thought that a deuteration experiment might shed some light as to which protons on pyrrolidinone **233** are more acidic. Treatment with LDA (1.05 equiv.) at -78°C followed by addition of CD_3COOD (35 equiv.) and aqueous workup led to 14% deuteration at the 4 position only (Figure 15). This percentage was rather low and could be attributed to D/H exchange in the workup. Treatment with only CD_3COOD (150 equiv.) in $CDCl_3$, in an NMR tube gave no D-exchange even after two days and treatment with ^tBuONa (1.0 equiv.) and then CD_3COOD (35 equiv.) gave decomposition of the starting material. Finally, treatment with NaH (1.10 equiv.) in THF, followed by addition of CD_3COOD (7.1 equiv.) and no aqueous workup, gave 47% deuteration at the 4 position as well as 16% at the 5 and 22% at the 3 position (Figure 15). This indicates that, even though the acidity of the proton α to the nitro group is greater than the others, deprotonation still occurs on other positions when the pyrrolidinone is treated with base.

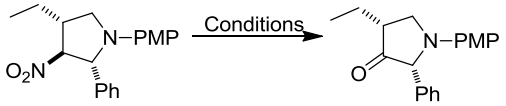


233

Figure 15

Due to the problems associated with attempted Nef reactions on pyrrolidinone **233**, it was decided to study the reactivity of its reduction product, pyrrolidine **247**, in the same reactions to give the ketone **301**. Pyrrolidine **247** was obtained from a borane reduction of **233** (Scheme 81, section 2.1),[116] and lacking a carbonyl in the C^2 position might be less prone to degradation. Many methods were attempted for this modification, but the reactions were unsuccessful (Table 5).

Table 5. Attempts of a Nef reaction of pyrrolidine **247**



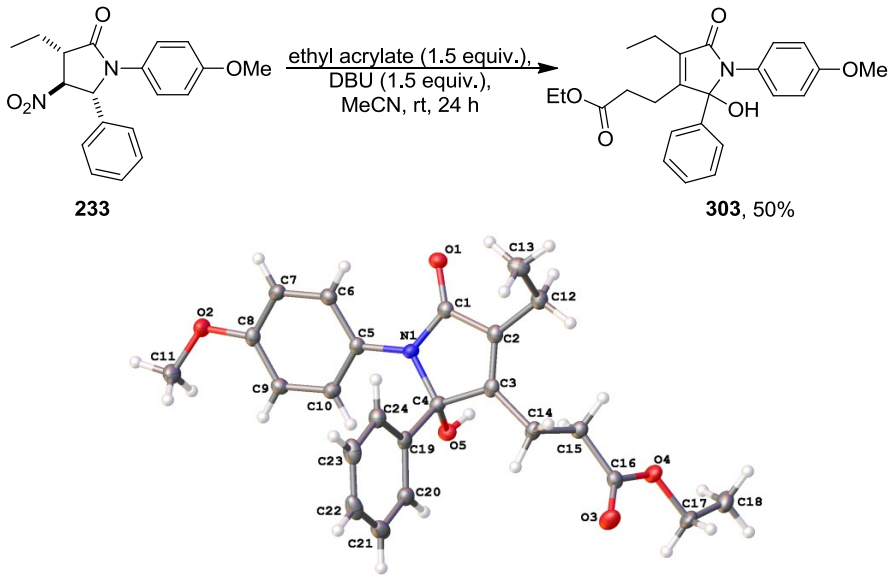
247 **301**

Entry	Reagents/Conditions	Result
1	EtONa (2 equiv.), EtOH, then H_2SO_4	Recovered sm
2	$CrCl_2$, MeOH/EtOAc, reflux	Degradation
3	$TiCl_3$, pH = 5 buffer, THF/H_2O, rt	Recovered sm
4	CAN, MeCN/H_2O, Et_3N, 60 ^oC	Recovered sm
5	DBU (2 equiv.), MeCN, rt, 13 days	Degradation
6	DBU (2 equiv.), MeCN, 60 ^oC, 3 days	Recovered sm

Moreover, it has been shown that nitro groups γ to a carbonyl can eliminate HNO_2 on treatment with base to give an enone.[78] However, treatment with both DBU (5.00 equiv.) in MeCN at reflux and Et_3N (10.0 equiv.) in toluene at reflux, led to decomposition without any sign of the enone by NMR, while the use of fewer equivalents of amine and lower temperatures gave no reaction.

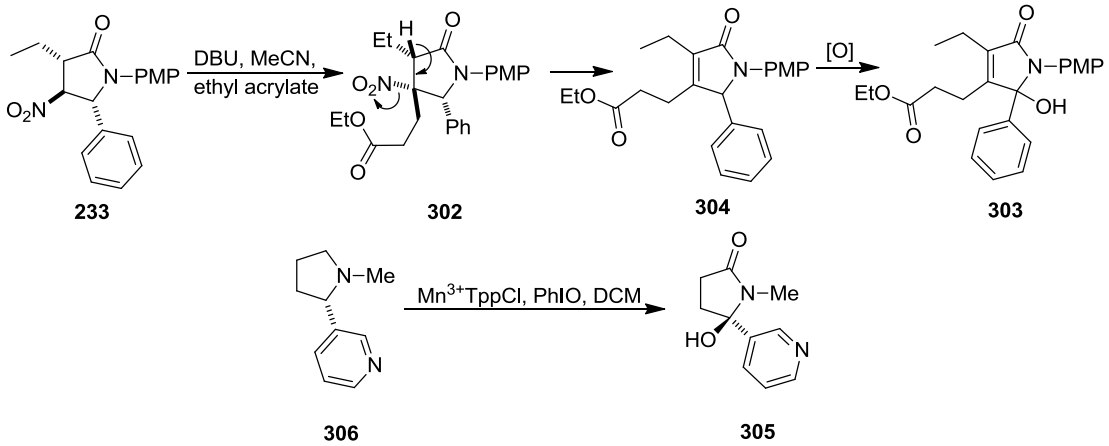
2.3.9.2 Reactions of pyrrolidinone 233 with electrophiles

Further functionalisation of pyrrolidinone **233** α to the nitro group by reaction with electrophiles was pursued. Deprotonation at the C^4 position followed by Michael addition to ethyl acrylate was first attempted. When **233** reacted with DBU (1.50 equiv.) and ethyl acrylate (1.50 equiv.) in MeCN at room temperature,[145] the 1,4-addition product **302** was not isolated, but the unexpected elimination product **303** was obtained in 50% yield instead (Scheme 103). The unexpected 1*H*-pyrrol-2(5*H*)-one **303** was a crystalline solid and its structure was determined by X-ray crystallography (Scheme 103).



Scheme 103. Synthesis and X-ray crystal structure of **303**

A tentative mechanism for the synthesis of this product is presented in Scheme 104. Presuming that a Michael addition first occurs to afford the expected product **302** that in the presence of base eliminates HNO_2 to give enone **304**. DBU has been shown to affect ionic denitrations on nitroalkanes by elimination of HNO_2 (Scheme 56, section 1.3.3). Finally, an unexpected oxidation occurs at the C^5 position of **304**, presumably from molecular oxygen, to give product **303**. To our knowledge only one example of such an oxidation has been reported by Chauncey and Ninomiya.[146] The authors observed product **305** whilst studying the biomimetic oxidation of nicotine (**306**) using metalloporphyrin catalysts and iodosobenzene as the oxidant (Scheme 104).

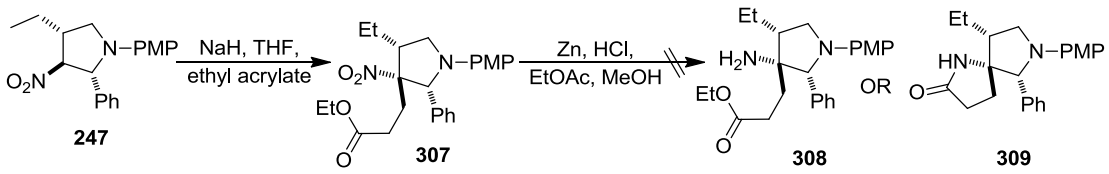


Scheme 104. Mechanism for the formation of **303**

The similar reaction of pyrrolidinone **233** with DIPEA (2.00 equiv.) and ethyl acrylate (up to 10.0 equiv.) gave no product, while treatment with LDA (1.05 equiv.) in THF

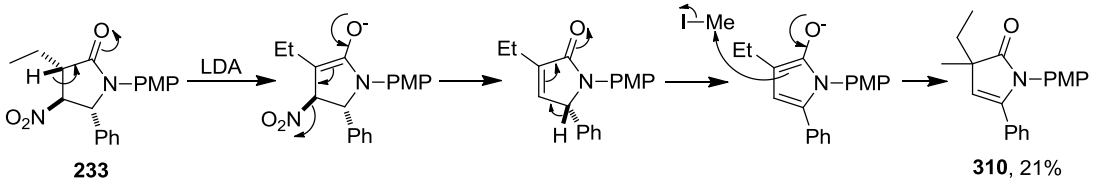
at -78°C, followed by addition of ethyl acrylate (1.50-10.0 equiv.), gave a complex product mixture. Furthermore, reaction of **233** with LDA (1.20 equiv.) and the more electrophilic acrolein (5.00 equiv.) also gave a complicated reaction mixture.

It was also attempted to react pyrrolidine **247** with ethyl acrylate, hoping that the absence of a carbonyl in the molecule would make the addition product more stable. Deprotonation with NaH (1.10 equiv.), followed by reaction with ethyl acrylate (2.00 equiv.) in THF at rt, was slow. The starting material was consumed after 19 h and what appeared to be pyrrolidine **307** by ^{1}H NMR was isolated in a crude form (Scheme 105). However, the product was found to be unstable to chromatography and to storage even at -5 °C. Among the degradation products was the starting pyrrolidine **247**. In light of this instability, it was attempted to reduce the nitro group after the reaction and avoid isolating the unstable product **307**. This unfortunately gave only a complicated mixture of degradation products and none of the expected **308** and **309**.



Scheme 105. Reaction of pyrrolidine **247** with ethyl acrylate

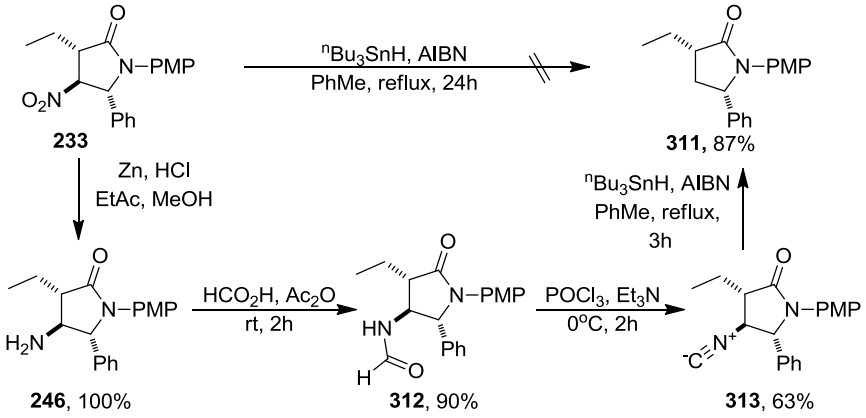
Finally, it was attempted to methylate the C^4 position of pyrrolidinone **233**. First the pyrrolidinone was reacted with MeI (4.00 equiv.) and K_2CO_3 (4.00 equiv.) in acetone at reflux, however this led to decomposition of the starting material. Treatment of the pyrrolidinone with LDA (1.20 equiv.) in THF at -78 °C, followed by addition of MeI (3.50 equiv.) and stirring at room temperature, gave a mixture of products with only one being less polar that the starting material. The structure deduced from the spectroscopic analysis was that of compound **310** (Scheme 106), isolated in 21% yield. A possible mechanism for its formation involves first elimination of HNO_2 and then methylation by MeI at the C^3 position, to give product **310**.



Scheme 106. Reaction of **233** with MeI

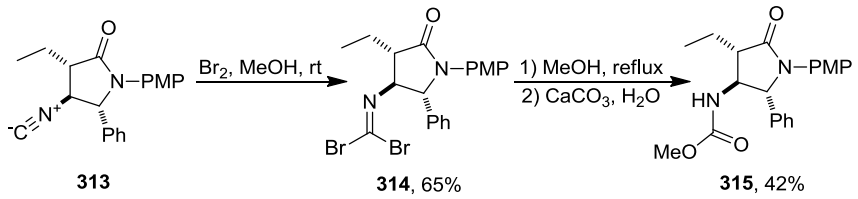
2.3.9.3 Denitration

A useful modification of pyrrolidinone **233** would be the complete removal of the nitro group (denitration). Such denitrations have been reported to occur *via* a radical method using Bu_3SnH and an initiator.[77] Heating a solution of **233** at 80°C in dry degassed toluene with Bu_3SnH (5.00 equiv.) and AIBN (1.00 equiv.), led to incomplete consumption of the starting material in 24 h. Use of ABCN as an initiator,[147] led to a faster reaction and a complete consumption of the starting material in 24 h, however it gave a complicated product mixture with very small amounts of possible denitrated product observed by ^{1}H NMR. There is some indication based on ^{1}H NMR for the presence of an oxime in the product mixture, however this has not been confirmed due to instability of the products. Consequently, another lengthier route to product **311** was investigated (Scheme 107). This route proved to be successful and most steps were high yielding. Moreover, it allowed to gain access to formamide **312** and isocyanide **313**, which could be useful for the synthesis of other derivatives.



Scheme 107. Four-step denitration sequence

As isocyanides are versatile precursors to other functional groups, it was decided to investigate these. Use of bromine in methanol has been shown to give carbamates from isocyanides,[148] however simple stirring of **313** with Br_2/MeOH at rt gave dibromide **314** in 65% yield. These dibromides are the suspected intermediates to this transformation, so the formation of **314** is not unexpected. Refluxing the reaction mixture for 15 h gave the desired carbamate **315** in 42% yield (Scheme 108).

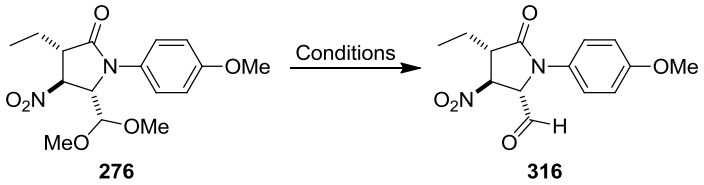


Scheme 108. Reactions of isocyanate **313**

2.3.9.4 Modification of the C^5 substituent, acetal hydrolysis

The synthesis of aldehyde **316** would be very useful as that would open the road to new functionalisations of the pyrrolidinone scaffold, which could lead to the synthesis of interesting molecules. After the successful synthesis of pyrrolidinone **276** it was attempted to hydrolyse the acetal group to obtain aldehyde **316**. A number of methods were attempted, however so far it has not been possible to isolate **316** (Table 6).

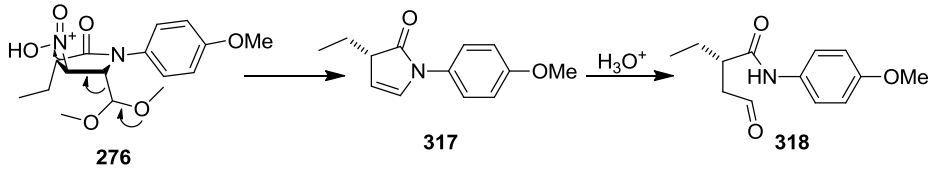
Table 6. Attempts of acetal hydrolysis of **276**



Entry	Reagents/Conditions	Result
1	Amberlyst-15, Acetone/H_2O, rt and reflux[149]	Recovered sm
2	Acetone, HCl 2M (10.0 equiv.), rt	Recovered sm
3	DCM/ H_2O, *p*-TSA, rt and reflux[150]	Recovered sm
4	MeOH, H_2SO_4 1M (2.50 equiv.), rt and reflux	Recovered sm
5	THF, H_2SO_4 1M (5.00 equiv.), reflux	Recovered sm
6	THF, H_2SO_4 2M (10.0 equiv.), reflux, 3 days	Recovered sm
7	DMSO, H_2SO_4 2M (10.0 equiv.), reflux	Degradation, trace of aldehyde
8	$TiCl_4$, LiI, Et_2O, rt	Rec. sm, trace of aldehyde
9	$FeCl_3/SiO_2$, $CHCl_3$, rt[151]	Recovered sm
10	$FeCl_3/SiO_2$, $CHCl_3$, formaldehyde, reflux[152]	Recovered sm
11	HCO_2H neat	Recovered sm

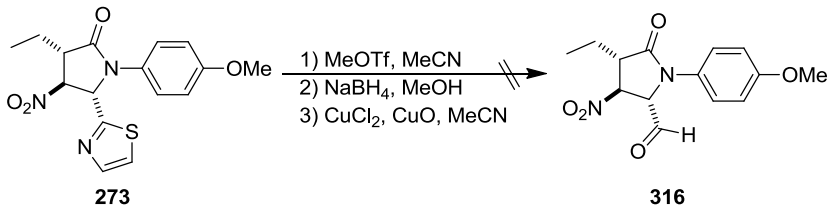
12	TMSI (2.00 equiv.), DCM, rt[153]	Rec. sm, trace of aldehyde
13	BBr_3 (4.00 equiv.), DCM, rt[154]	Degradation

The results show that acetal **276** was very inert to deprotection and when harsher conditions were used degradation occurred. A possible explanation for this seems to lie on the structure of **276**. The presence of the nitro group β to the acetal in an *anti*-parallel arrangement should make it prone to elimination at strongly acidic conditions. Possible protonation of the nitro group might lead to the elimination shown in Scheme 109, giving enamine **317** that can then hydrolyse to aldehyde **318**, which could degrade further.



Scheme 109. Degradation of acetal **276**

In light of this poor result, a different way to access the desirable aldehyde **316** was sought. The Dondoni reaction is a known method to transform a thiazole group to an aldehyde group and has found various applications in synthesis.[155] Since thiazole substituted pyrrolidinone **273** was previously synthesised, we investigated whether this could be a possible precursor to aldehyde **316**. However, when thiazole **273** was subjected to the reaction conditions (Scheme 110), only a trace of aldehyde **316** (<10%) was seen in ^{1}H NMR spectroscopy.

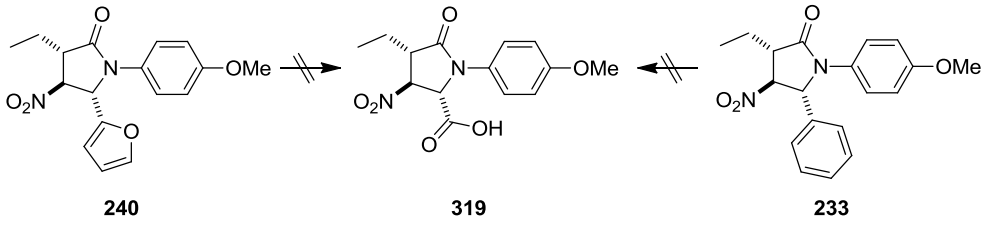


Scheme 110. Attempt of a Dondoni reaction

2.3.9.5 Modification of the C^5 substituent, synthesis of proline analogue 319.

A desirable modification would be to have a carboxylic acid substituent at the C^5 position of pyrrolidinone **232**, as that will effectively be an analogue of proline, which would increase the potential for biological activity. Firstly, the oxidation of an

aromatic substituent at C^5 to a carboxylic acid was studied. The oxidation of aromatic groups to carboxylic acids has been reported by Sharpless and co-workers.[156] The procedure uses a catalytic amount of $RuCl_3$ which forms the active oxidant RuO_4 in the presence of HIO_4 as the stoichiometric oxidant, in a biphasic solvent system (CCl_4/MeCN/H_2O).[157] However the reaction was not successful for pyrrolidinone **233** and led to decomposition. In another publication, Plietker showed that a furan group could be oxidized to a carboxylic acid using $RuCl_3$ and oxone, which was for them an unwanted side reaction in the ketohydroxylation of alkenes.[158] The same reaction conditions were used with the furan pyrrolidinone **240** (Scheme 111) but were ineffective, leading to recovery of the starting material.



240 **319** **233**

Scheme 111. Synthesis of carboxylic acid **319** by oxidation of the C^5 substituent

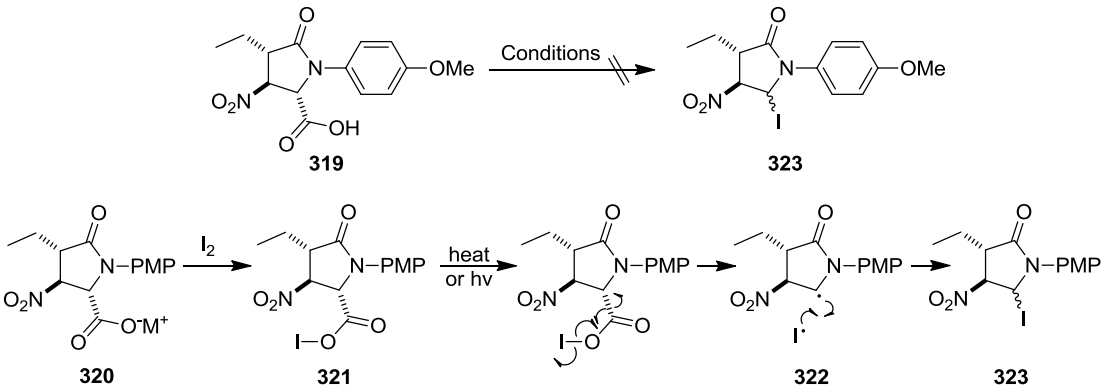
In light of this poor result, it was decided to look at obtaining carboxylic acid **319** from a simpler source, ester **242**. Indeed, hydrolysis of this ester was successful in non basic conditions, using either the mild reagent Me_3SnOH[159] or simply refluxing in HCl/Acetone (Scheme 112).

231 **242** **319**

Scheme 112. Synthesis of carboxylic acid **319** by ester hydrolysis of **242**

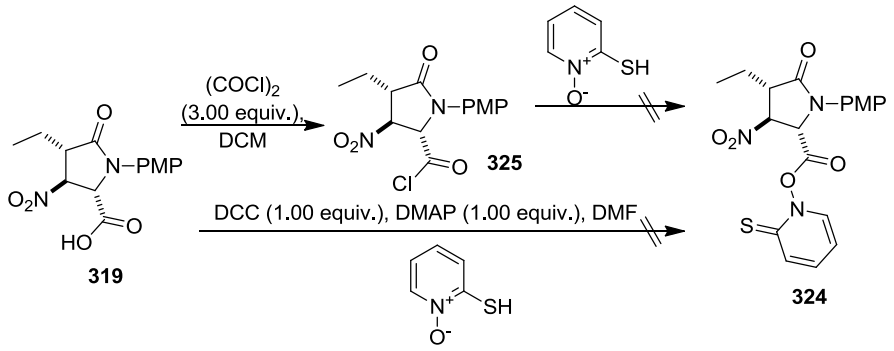
Having synthesised carboxylic acid **319**, we looked at the possibility of decarboxylation that would give access to new derivatives. We first looked at simply heating, to induce loss of CO_2. Whereas reflux in toluene gave recovered starting material, reflux with xylene at 140 ^oC led to degradation. The Hunsdiecker reaction was also investigated. In this reaction, a carboxylate salt **320** with a soft metal (Hg, Ag) is first formed and subsequent reaction with iodine gives iodide **321** bearing an O-I bond.[160] Under the influence of light or heat this decomposes to release CO_2 and

give radical **322**, which then reacts with a radical iodide to give iodide **323** (Scheme 113). Two sets of conditions were tested, treatment with $Pd(OAc)_4$ and I_2 in CCl_4 under UV light,[160] and treatment with HgO and I_2 in Toluene, at reflux,[161] both with no success (Scheme 113).



Scheme 113. Mechanism of the Hunsdiecker reaction

Moreover, it was attempted to form the Barton ester of acid **324** and then affect a radical decarboxylation. Efforts to synthesise this ester either by formation of acid chloride **325** and then reaction with 2-mercaptopyridine *N*-oxide,[162] or by coupling with DCC or EDC in the presence of DMAP, failed to give the desired ester **324** (Scheme 114).

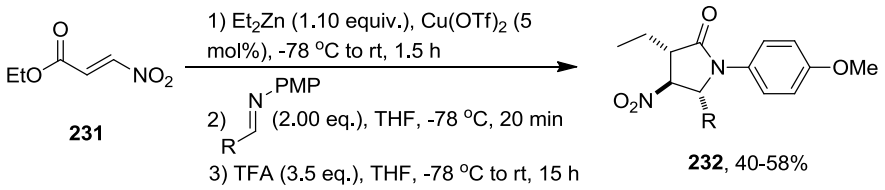


Scheme 114. Attempts to synthesise Barton ester **324**

2.3.10 Conclusions

This chapter described further developments in the 1,4-addition/nitro-Mannich/lactamisation reaction sequence from nitroacrylate **231**. Using the developed reaction conditions, the synthesis of 10 new analogues of pyrrolidinones **232**, was accomplished (Scheme 115). The limitations of this methodology, in reactions with

heterocyclic and alkyl PMP-protected imines were investigated, as well as with the use of alternative dialkylzinc reagents Ph_2Zn and $^{i}Pr_2Zn$.



Scheme 115. Synthesis of pyrrolidinones **232**

Furthermore, an enantioselective variant of this reaction was successfully developed, by utilising the reported method for asymmetric conjugate addition of dialkylzinc reagents to nitroalkenes as part of our one pot procedure.[130] By synthesising phosphoramidite ligand **294**[130] and using it as our chiral catalyst, a good enantioselectivity for pyrrolidinones **233** and **241** (89% *ee*, 99% *ee* after recrystallisation, Figure 16) was obtained. Furthermore, an X-ray crystal structure of **287** was successfully obtained, that showed us the absolute stereochemistry of pyrrolidinone **241** and therefore of the initial 1,4-addition product **300**.

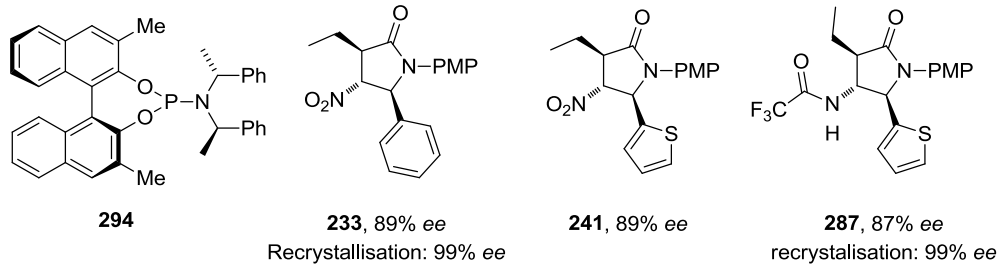


Figure 16

Finally, some functionalisations of selected pyrrolidinones were investigated. It has been possible to obtain isocyanate **313**, deamination product **311** and proline analogue **319** (Figure 17), interconversions that prove the usability of the pyrrolidinone structure produced as a building block for the synthesis of useful molecules. Moreover, some unexpected products such as **310** and **303** were isolated (Figure 17), providing some knowledge on the reactivity of pyrrolidinones **232** and their tolerance to a variety of conditions and reagents.

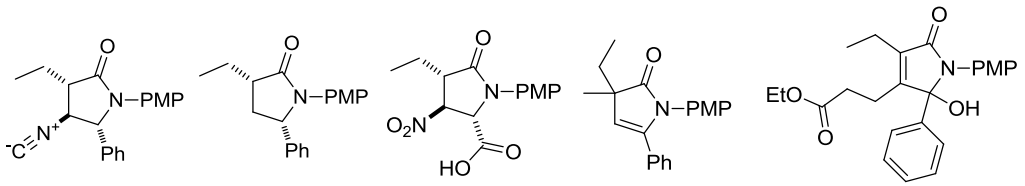


Figure 17

2.3.11 Future work

The synthesis of pyrrolidinones **232** in an efficient one pot 3-step cascade was demonstrated. The pyrrolidinones produced were densely functionalised and diastereomerically pure. Furthermore, a number of possible functional group interconversions in the pyrrolidinone core have been successful.[116] This opens up the way for using our methodology in the synthesis of more complex molecules. A few molecules bearing the same stereochemistry around the pyrrolidine core have been identified. These include proteasome inhibitor **195**,[163] the dietary supplement pyroglutamic acid **193**, nicotine metabolite cotinine **194** and the experimental human neutrophil elastase inhibitor **326** (Figure 18).[164] The work towards the synthesis of **326** is presented in the following chapter 2.5.

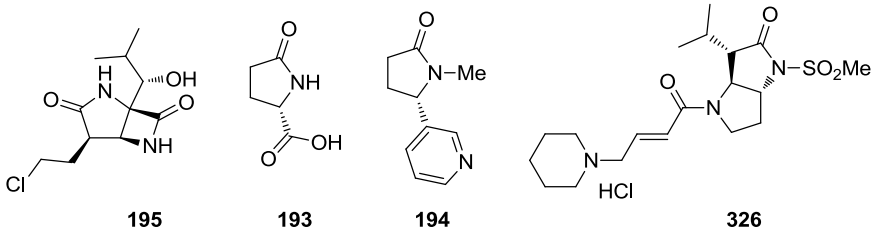


Figure 18

Moreover, up to the present time the 1,4-addition/nitro-Mannich methodology has been limited to the use of dialkylzinc and hydride reagents in doing the conjugate addition step. However, a number of heteroatom nucleophiles are known to add to nitro-alkenes.[39] Successfully using a non-zinc nucleophile and especially a heteroatom as part of our methodology, would greatly increase its versatility and applications in the synthesis of useful molecules. The reactions of nitroacrylate **231** and *β*-nitrostyrene with a variety of carbon, oxygen, nitrogen, sulphur and phosphorus nucleophiles, have been investigated and are presented in chapter 2.5.

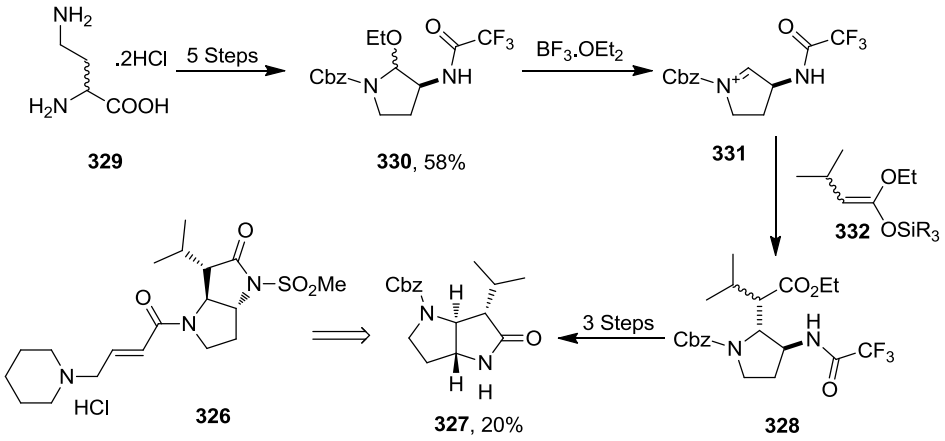
2.4 Towards the synthesis of a human neutrophil elastase inhibitor (GW311616A)

2.4.1 Precedence and methodology

An important target of this project was to use the developed methodology to access a useful molecule, natural product or pharmaceutical. One such molecule is the human neutrophil elastase inhibitor **326**. This pharmaceutical, was found to be active for the treatment of chronic bronchitis and is currently made from the precursor **327** (Scheme 116).[165]

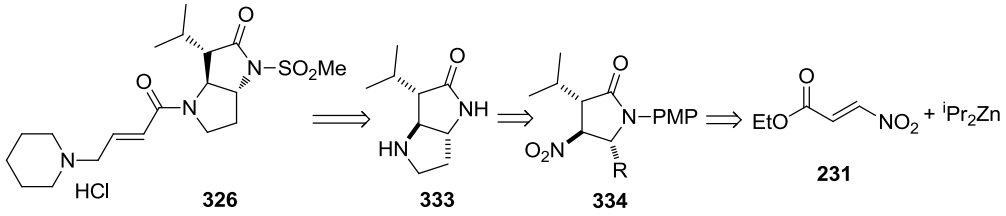
Research in GlaxoWellcome on identifying serine protease inhibitors, has discovered that 5,5-*trans*-fused systems showed inhibitory activity. The systems studied were pyrrolidine-*trans*-lactones[166] and pyrrolidine-*trans*-lactams,[167] found to be active for several proteases such as chymotrypsin, thrombin, cathepsin G, trypsin, and human neutrophil elastase (HNE). The later, HNE is thought to be involved in respiratory diseases such as asthma and chronic bronchitis. Lactam **326** was found to have improved activity and bioavailability compared to previous studies.[164]
This compound has been synthesised in an overall chemical yield of 1.3% in a 14 step synthesis.[164] The authors first attempted a racemic synthesis, where key intermediate **328** could be accessed by synthesising first the disubstituted pyrrolidine ring and then using acyliminium chemistry to introduce the isopropyl group in a diastereoselective manner. The synthesis started from commercially available 2,4-diaminobutyric acid **329** that gave pyrrolidine **330** in five steps with 59% overall yield (Scheme 116). Pyrrolidine **330** could then lead to acyliminium cation **331** after treatment with a Lewis acid. Subsequent reaction with commercially available acetal **332** gave pyrrolidine **328**, which in two more steps afforded the desirable **327** in 20% yield. The racemic synthesis had an overall yield of 12% over eight steps.

Two asymmetric syntheses were also developed starting from commercial *R*-asparagine or *R*-methionine. Enantiomerically pure **326**, was synthesised in 7% overall yield from *R*-asparagine in nine steps, while a yield of 5% over nine steps was obtained from *R*-methionine (Scheme 116).



Scheme 116. Synthesis of GW311616A (**326**)[164]

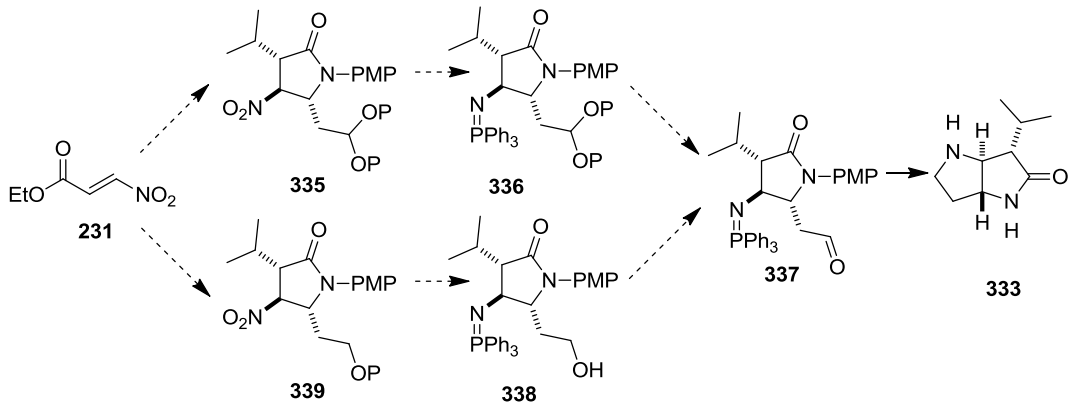
Pyrrolidinone **326** can easily be formed from precursor **333**, which has an *anti*/*anti* stereochemistry around the pyrrolidinone ring. Assuming that the amine nitrogen is derived from reduction of the nitro group, then pyrrolidinone **334** can be a suitable precursor to **333**. The pyrrolidine and pyrrolidinone rings are however *trans*-fused, something that would make it difficult to synthesise compound **333** starting from a pyrrolidinone like **334** (Scheme 117). Very few methods for making *trans*-fused octahydropentalenes exist, due to the ring strain in this system.[168,169] Nonetheless, it was felt that we could overcome these problems by either of the two synthetic strategies described below.



Scheme 117. Retrosynthetic analysis of **326**

The first synthetic strategy to synthesise the desired bicyclic pyrrolidinone **333**, involved accessing protected aldehyde **335** through the nitro-Mannich methodology described in section 2.3. Phosphorane imine **336**, could then be formed from the nitro group after a reduction and subsequent reaction with DEAD and Ph_3P.[170] Subsequent release of aldehyde **337** and aza-Wittig reaction should yield the desired compound **333** (Scheme 118). Intramolecular aza-Wittig reactions have previously been used to make strained five-membered rings.[171] Moreover, Taylor and co-workers have reported Tandem oxidation processes to perform the oxidation of an alcohol and

subsequent Wittig reaction in one pot.[172] Hence this could avoid the need to isolate aldehyde **337** and make alcohol **338**, derived from protected alcohol **339**, also a good starting material for the aza-Wittig reaction (Scheme 118).



Scheme 118. Two possible routes to pyrrolidinone **333**

Alternatively, the most obvious way to make pyrrolidinone **333**, would be the simple intramolecular nucleophilic addition or substitution reaction of the free amine, derived from the nitro group, onto a carbon bearing a suitable leaving group (**340**) or a suitable electrophile on the C^5 substituent (**341**). This could be either a tosylate, mesylate or simply an aldehyde (Figure 19). Moreover, an alkene like **342** could be used to perform a haloamination (after first reducing the nitro group) and the halogen subsequently removed with radical dehalogenation.

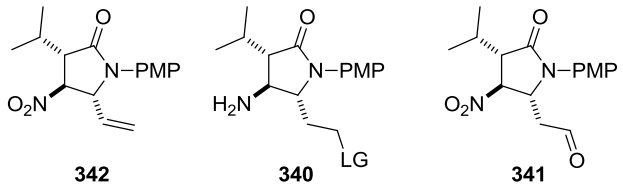


Figure 19. Possible precursors to **333**

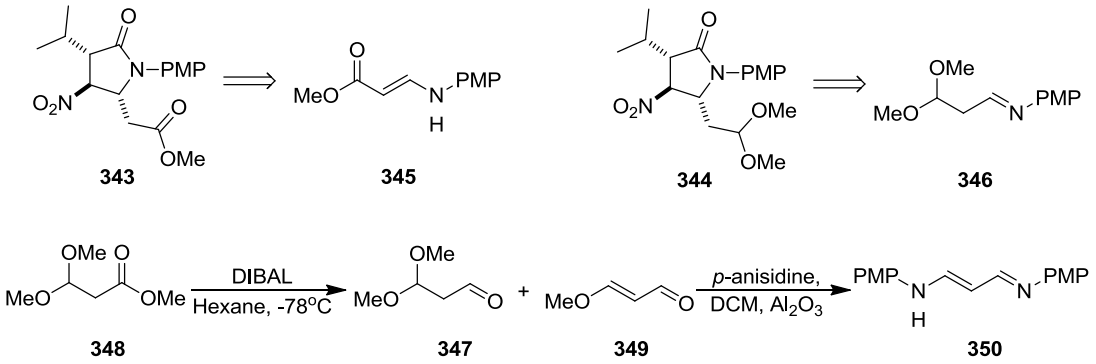
2.4.2 Investigation of the synthesis

Diisopropylzinc has already been shown to be successful in the synthesis of pyrrolidinone **282** (Scheme 91, section 2.3.3). More intriguing would be the selection of a suitable imine that would give a useful functionality at the C^5 position of our pyrrolidinone scaffold.

Initially, the synthesis of pyrrolidinones **343** and **344** was investigated, as those would be useful starting points for our investigation (Scheme 119). The imine required for

the synthesis of pyrrolidinone **343** exists only in the enamine form **345**. Even though it is known that enamines do not react directly in the nitro-Mannich reaction, in this particular example, the α position to the nitrogen should still be electrophilic due to conjugation with the ester function. Unfortunately, nitro-Mannich experiments revealed that no isolation of any pyrrolidinone product from this reaction, which gave a complicated mixture of products.

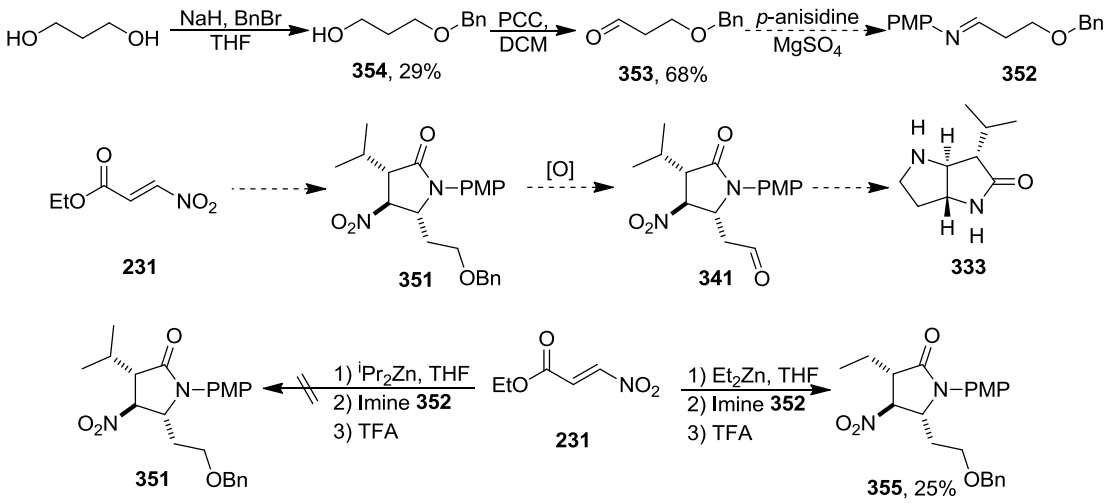
Synthesis of pyrrolidinone **344** requires access to imine **346**. The required aldehyde **347** was not commercially available though, so it was attempted to synthesise aldehyde **347** from a DIBAL reduction of commercially available ester **348** (Scheme 119). The DIBAL reduction gave a mixture of aldehydes **347** and **349**. Disappointingly though, when the mixture of the two aldehydes was reacted with *para*-anisidine, the only product isolated from the reaction was imine **350**. Nitro-Mannich reaction of imine **350** gave a complicated mixture of products (Scheme 119).



Scheme 119. Attempts to synthesise pyrrolidinones **343** and **344**

In view of this failure to synthesise pyrrolidinones **343** and **344**, a different route to aldehyde **341** *via* the protected alcohol **351** was investigated. To access the necessary imine **352**, aldehyde **353** was synthesised in two steps from 1,3-propanediol (Scheme 120).[173] It was however not possible to isolate imine **352**, when **341** reacted with *para*-anisidine, in DCM, both with $MgSO_4$ at rt and with Al_2O_3 at -78 ^oC. Nevertheless, it was attempted to synthesise pyrrolidinone **355**, by *in situ* forming imine **352** at -78 ^oC and maintaining the cold temperature while the solution of imine was transferred into the solution of the nitronate, derived from **231** and diethylzinc. With this method it was possible to isolate pyrrolidinone **355** in 25% yield. Disappointingly though, none of pyrrolidinone **351** was isolated from the reaction with diisopropylzinc. The instability of imine **352** and its poor reactivity as seen

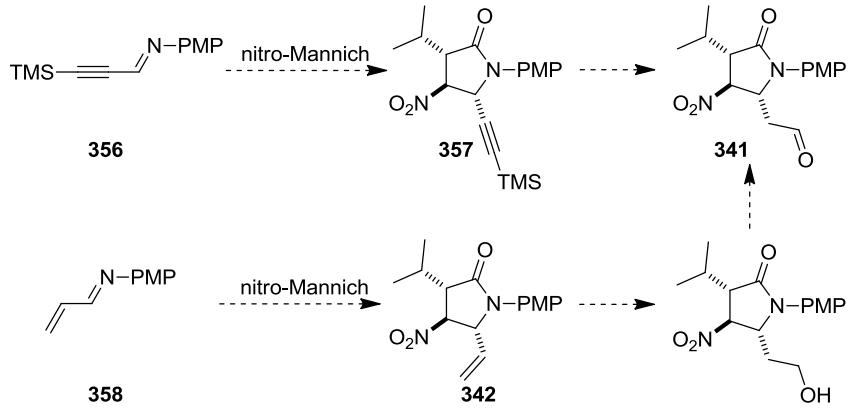
before for alkyl imines (section 2.3.2) is tentatively caused by its isomerisation to an enamine that would not be reactive in the nitro-Mannich reaction and could polymerise.



Scheme 120. Use of imine **352** in the synthesis of pyrrolidinones

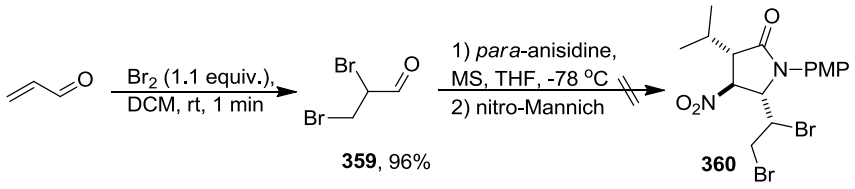
Some unsaturated imines were then examined as a way towards pyrrolidinones **341** and **342**. Imine **356** was easy to synthesise ($MgSO_4$, DCM, 0 ^oC, 1 h), but unfortunately the nitro-Mannich reaction gave none of the desired pyrrolidinone **357** (Scheme 121). Instead, only 1,4-addition product, unreacted imine and degradation products were isolated, presumably due to side reactions such as polymerisation.

On the other hand, imine **358** (derived from acrolein) could not be isolated. When acrolein reacted with *para*-anisidine, in DCM, both with Al_2O_3 at rt and with Al_2O_3 at -78 ^oC, only degradation products were observed using ^1H NMR. Nevertheless, it was possible that some of the imine is produced at -78 ^oC and degrades at higher temperatures and/or workup (as seen above with imine **352**). It was therefore attempted to make pyrrolidinone **342** by synthesizing imine **358** *in situ* at -78 ^oC (THF, molecular sieves) and transfer the solution of imine into the reaction mixture while maintaining the cold temperature. This again was not successful.



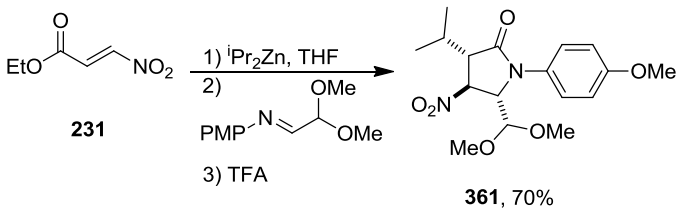
Scheme 121. Other routes to aldehyde **341**

Moreover, it was envisaged that protection of the double bond of acrolein or its conversion to a less reactive functionality, might facilitate the synthesis of a useful pyrrolidinone precursor. The reaction of acrolein with bromine was investigated.[174] Acrolein reacted fast with 1.1 equiv. of bromine to give dibromide **359** quantitavely. Unfortunately, the *in situ* formation of imine and nitro-Mannich reaction gave none of pyrrolidinone **360** (Scheme 122).



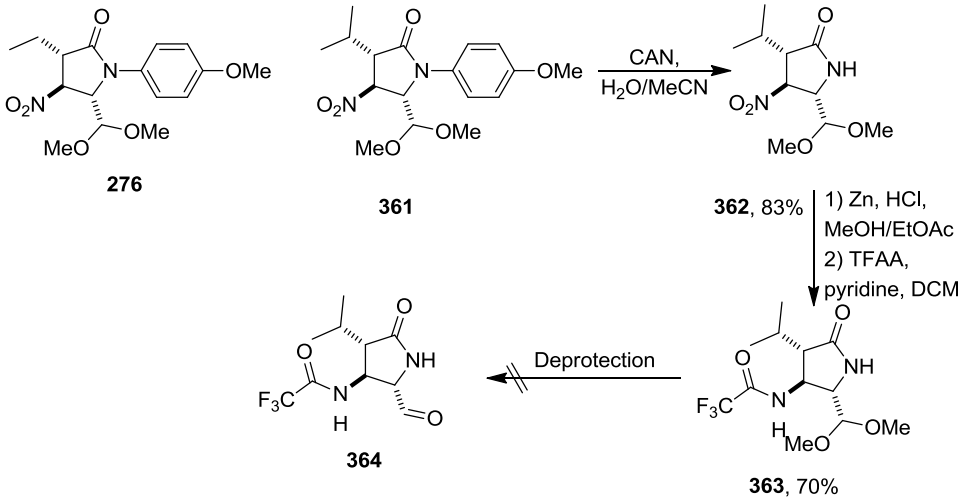
Scheme 122. Attempt to synthesis pyrrolidinone **360** from imine **359**

Even though it would be preferable for the C^5 substituent on pyrrolidinone scaffold **334** to be two-carbon atoms long, it was not possible to isolate any such pyrrolidinone in reasonable quantities. In light of that, the use of single carbon substituents was investigated, with the aim of extending the carbon chain by one carbon before cyclisation. Pyrrolidinones bearing a one-carbon C^5 substituent have been synthesised successfully before (section 2.3.2). The synthesis of pyrrolidinone **361** using acetal imine **267** was initially investigated (Scheme 123). The acetal protected pyrrolidinone **361** was made successfully in 70% yield.



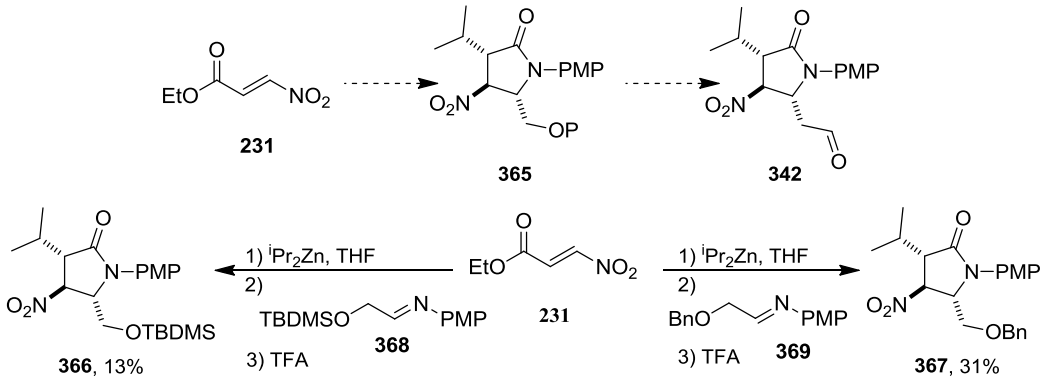
Scheme 123. Synthesis of acetal **361**

However, to do any useful chemistry with pyrrolidinone **361**, it was required to deprotect the acetal group to the free aldehyde. A similar deprotection was attempted before with pyrrolidinone **276** and was unsuccessful (section 2.3.9.4), so **361** was expected to also be hard to deprotect. In knowledge of this, a different deprotection route was investigated this time. First the PMP protecting group was removed to give **362** and then the nitro group was reduced and protected as a trifluoroacetamide, to give pyrrolidinone **363** in good yield (Scheme 124). It was then attempted to deprotect the acetal group in pyrrolidinone **363** by standard methods. Reaction with HCl/Acetone/reflux gave only a complicated mixture of products in which only traces of starting material were identified, as did reaction with TMSI (Scheme 124). This was similar to problems encountered earlier with a similar deprotection (section 2.3.9.4) and could be attributed to the trifluoroacetamide group being a good leaving group like the nitro group.



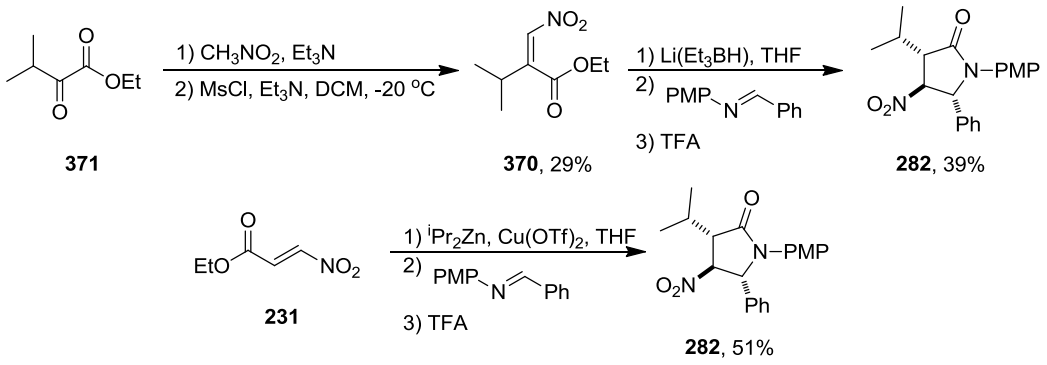
Scheme 124. Attempts of acetal hydrolysis

In light of these results, it was decided to avoid synthesising aldehyde **364** altogether and synthesise instead a protected primary alcohol **365**, that could also potentially be chain extended to aldehyde **341** (Scheme 125). The synthesis of two such pyrrolidinones, **366** and **367** was investigated. Not surprisingly, the corresponding imines **368** and **369** were found to be unstable at room temperature, so were prepared at -78 ^{o}C and used *in situ*. The two pyrrolidinones **366** and **367** were isolated successfully, albeit in low yields, 13% and 31% respectively (Scheme 125).



Scheme 125. Synthesis of pyrrolidinones **366** and **367**

In light of the low yields of compounds **366** and **367** (too low to be the first step in a linear synthesis), another route to pyrrolidinones of this type was investigated. This route involved the use of nitroalkene **370** as the starting material, instead of nitroacrylate **231** and use of a hydride nucleophile (Superhydride®) instead of diisopropylzinc. Nitroalkene **370** was synthesised from ketoester **371** in 29% yield over two steps (Scheme 126).[175] To test if this was a better alternative to our current method it was first attempted to synthesise pyrrolidinone **282** and compare the results. Unfortunately, the yield of product **282** was lower than with the previous method (section 2.3.3) and the reaction slower, therefore this route was abandoned.

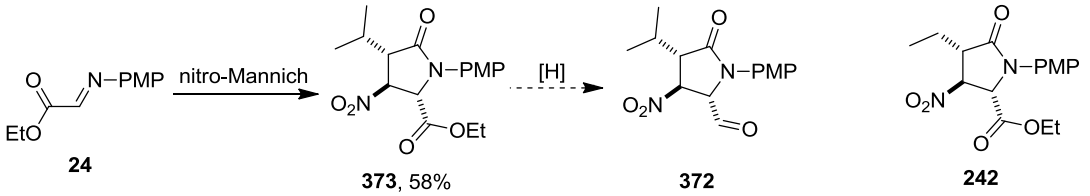


Scheme 126. Synthesis of pyrrolidinone **282** from nitroalkene **370**

Finally, the synthesis of aldehyde **372** was investigated, starting from ester **373**, which would require a selective reduction of the ester (Scheme 127). It is known that esters are easier to reduce than amides, as some reducing agents like borohydride salts have been reported to reduce ester groups, but do not reduce amides. However, pyrrolidinone **373** bears a lactam and an exocyclic ester group, which might reduce this difference in reactivity. Esters could be reduced to the corresponding alcohols using $NaBH_4$ in a refluxing methanol-THF mixture,[176,177] while these conditions were

shown to be tolerant to the presence of a nitro group. Moreover, the reduction of esters to aldehydes using 1.00 equiv. of DIBAL has been reported,[178] and has been widely used in synthesis, so it was felt that it could provide a selective reducing agent in our case too.

Ester **373** was successfully synthesised in 58% yield from imine **24**. However, due to the high cost of diisopropylzinc compared to diethylzinc it was decided to perform reduction studies on the similar ethyl analogue **242**, which was reported earlier.[119]

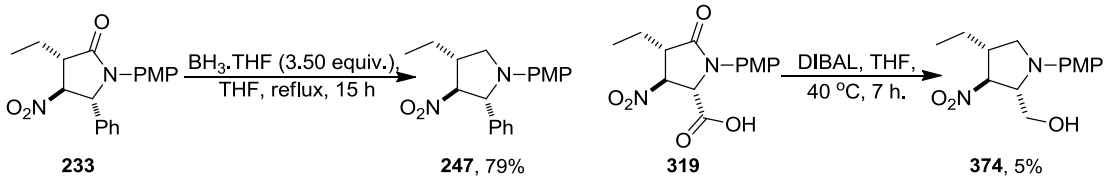


Scheme 127. Synthesis of ester **373**

Initially, reaction of ester **242** with DIBAL at -78 ^{o}C was attempted. When 1.00 equiv. of the reagent was used only starting material was observed after 1 h at -78 ^{o}C, as well as after warming to 0 ^{o}C. Using 2.00 equiv. of the reagent at -78 ^{o}C led to a complex mixture of products, from which only a small quantity of the starting material was observed. The reaction with sodium borohydride was then investigated. Refluxing a solution of ester **242** with $NaBH_4$ in MeOH/THF for 12 h, led to complete consumption of the starting material, however TLC and ^{1}H-NMR analysis showed a complex mixture of products.

In light of the poor results in the selective reduction of ester **242**, it was attempted to first hydrolyse to acid **319** (Scheme 112, section 2.3.9.5) and then investigate the selective reduction of the carboxylic acid group. The reduction of a carboxylic acid to an alcohol in mild conditions using $BH_3 \cdot SMe_2$ in THF, at rt has been reported,[179] and was found to be tolerant of the presence of a nitro group. Moreover, it is known from previous work that $BH_3 \cdot THF$ in refluxing THF is needed to reduce the amide of pyrrolidinone **233** to amine **247**, which suggests that the acid group is more reactive than the lactam group towards reduction with this reagent (Scheme 128).[116] When the reaction of acid **319** with 1.00 equiv. of $BH_3 \cdot SMe_2$ in THF, at rt was attempted, though, no product was observed after 4 h at rt. Switching to the more reactive $BH_3 \cdot THF$ (1.00 equiv.) led to consumption of the starting material in 2 h, giving only

a complex mixture of products. Furthermore, when acid **319** was deprotonated with sodium hydride and then treated with DIBAL 2.00 equiv. at -78 ^{o}C, no product was observed. Rising the temperature to rt still gave an incomplete reaction after 24 h, while heating to 40 ^{o}C led to consumption of the starting material after 7 h. However, the only product isolated at this temperature was alcohol **374** in a low yield (Scheme 128).



Scheme 128. Reduction of pyrrolidinones **233** and **319**

After the efforts of synthesising any useful intermediate to pyrrolidinone **333** were not successful, this investigation could not be continued due to time constraints and other lines of investigation.

2.4.3 Conclusions

This chapter described the work done towards the synthesis of bicyclic pyrrolidinone **333** starting from a suitable pyrrolidinone scaffold, accessed through our developed conjugate addition/nitro-Mannich/lactamisation method. Our initial efforts to synthesise a pyrrolidinone (**340**) bearing a two-carbon long substituent at C^5 position, did not give any satisfactory result. This failure was attributed to the poor reactivity of the corresponding imines in the nitro-Mannich reaction. Attempts to use an alternative route *via* a one carbon functional substituent at the same position, were also not promising. Although it was possible to synthesise acetal **361** in good yield, its deprotection to aldehyde **341** was not accomplished. Moreover, protected ethers **366** and **367** were isolated in low yields, therefore could not be used further in the synthesis sequence (Figure 20). Ester **373** was synthesised in good yield, however its selective reduction was not possible.

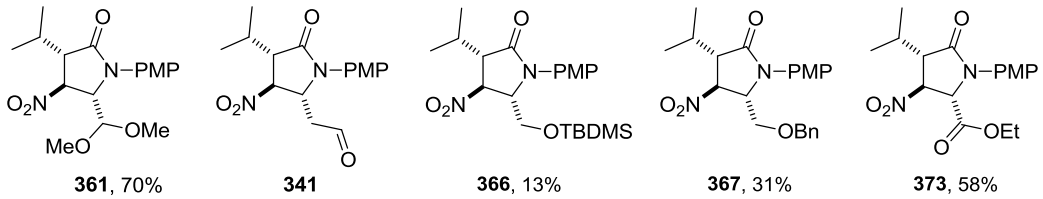
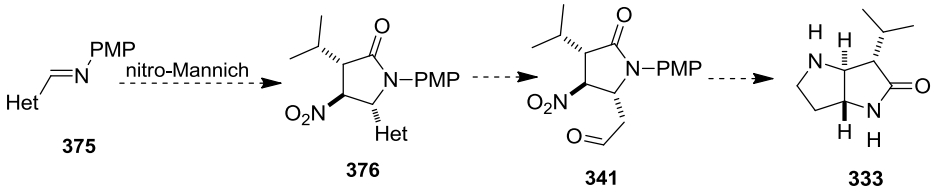


Figure 20

2.4.4 Future work

Our attempts to synthesise bicyclic pyrrolidinone **333**, starting from a suitable monocyclic pyrrolidinone, have so far been unsuccessful. The poor results of this investigation are due to the poor reactivity of the alkyl imines investigated, as well as the vulnerability of the pyrrolidinone core towards any modifications to the C^5 substituent. A possible solution to these problems would be to use a suitable heterocyclic imine **375** to synthesise the initial pyrrolidinone scaffold **376**. Pyrrolidinone **376** could then be transformed to the desirable aldehyde **341**. Consequent reduction of the nitro group of **341** should lead to cyclisation to form the desired **333** (Scheme 129).



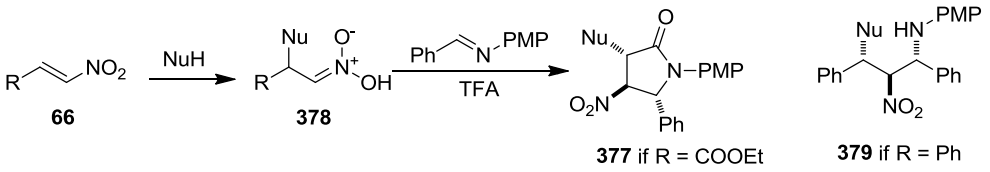
375 **376** **341** **333**

Scheme 129. Possible alternative route to **333**

2.5 The 1,4-addition/nitro-Mannich reaction of non-zinc nucleophiles on *β*-nitrostyrene

2.5.1 Precedence and methodology

One of the targets of this project was to investigate the use of nucleophiles, other than dialkylzinc reagents or hydrides, in a 1,4-addition reaction on nitroacrylate **231** and consequently a nitro-Mannich/lactamisation reaction to afford new pyrrolidinones **377**. Very few nitro-Mannich reactions exist in the literature, with a nitroalkane bearing a non-carbon group *β*- to the nitro group (Scheme 26, section 1.2.1). It was therefore desirable to investigate the reaction of nitroalkenes with heteroatom nucleophiles as well as more complex carbon nucleophiles, to give nitronates **378** that can then participate in the nitro-Mannich reaction (Scheme 130).



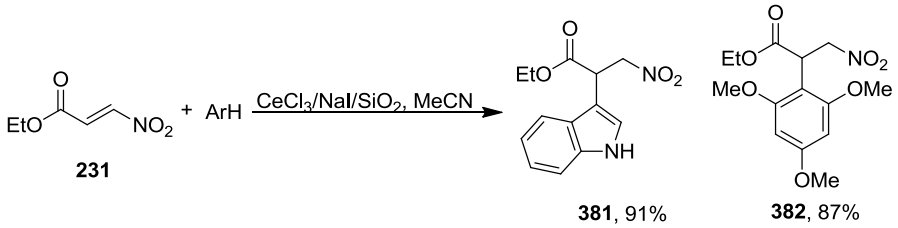
Scheme 130. Nitro-Mannich reaction with alternative nucleophiles

This methodology would yield highly functionalised structures like pyrrolidinones **377** and nitroamines **379**, increasing the scope of the nitro-Mannich reaction. Furthermore, possible modification of the Nu group in the final products could enable further use of this reaction in the synthesis of complex molecules. From the large number of possible nucleophiles, we concentrated on a representative sample of carbon, oxygen, nitrogen, sulfur and phosphorus nucleophiles. The scope of nitroalkenes that could be used is also large, however this investigation was limited to the reactions of nitroacrylate **231** and *β*-nitrostyrene **380**. Nitroacrylate **231** was chosen as it was already investigated in this thesis (section 2.2), while *β*-nitrostyrene **380** was chosen because it is commercially available and was widely used in previous studies.[35]

2.5.2 Investigation of 1,4-addition reactions to nitroacrylate 231

2.5.2.1 Carbon nucleophiles

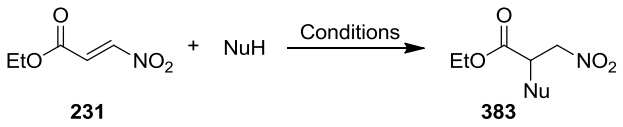
We first concentrated on the reaction of nitroacrylate **231** with carbon nucleophiles. Nitroacrylate **231** could act as a Friedel-Crafts reagent for electron-rich aromatics such as indole.[180] Simply stirring **231** with indole in DCM gave no reaction, but when the nitroalkene was activated by a mixture of $CeCl_3/NaI/SiO_2$, as it was reported, the 1,4-addition product **381** was isolated in good yield (Scheme 131).[180] The same conditions were found to be effective for 1,3,5-trimethoxybenzene, giving nitroalkane **382**.



Scheme 131. Reaction of nitroacrylate **231** with electron-rich aromatics

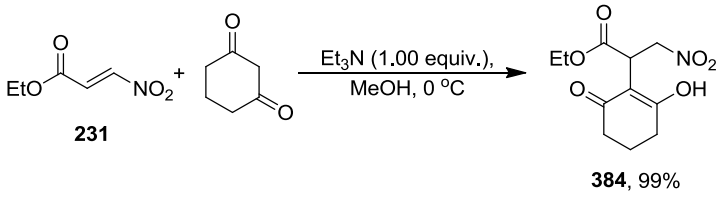
Some anionic nucleophiles were then investigated, begining with malononitrile, diethyl malonate and Meldrum's acid (Table 7). Disappointingly, most of those nucleophiles failed to give any desired 1,4-addition products **383**, as under a variety of conditions only degradation products were observed, presumably due to polymerisation.

Table 7. Michael additions of carbon nucleophiles



Entry	Nucleophile, Conditions	Result
1	Meldrum's acid, 2,6-Lutidine (10.0 mol %), THF	Degradation
2	Meldrum's acid, Toluene, reflux	No reaction
3	Malononitrile, proton sponge (10.0 mol %), THF	Degradation
4	Malononitrile, NaH (1.00 equiv.), THF	Degradation
5	Malononitrile, Toluene, reflux	No reaction
6	Malononitrile, DMF, proline (20.0 mol %)[181]	Degradation
7	Diethyl malonate, Et_3N (20.0 mol %), MeOH[182]	Degradation
8	1,3-Cyclohexanedione, Et_3N (1.00 equiv.), MeOH, 0 ^oC[183]	**384**, 99%

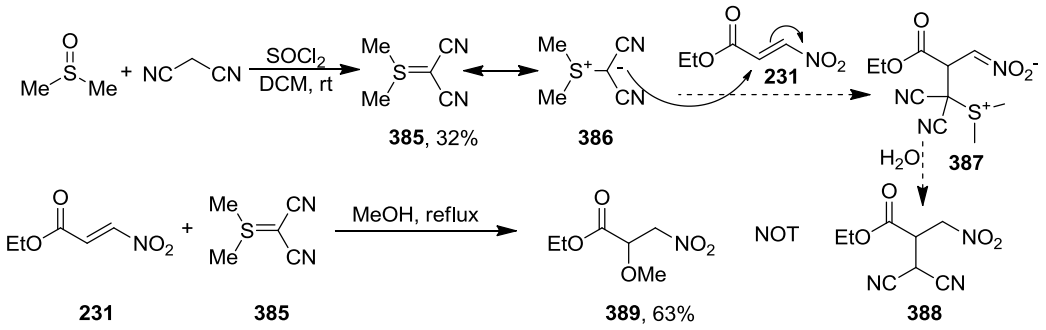
In contrast to the poor results from the other carbon nucleophiles, the reaction of 1,3-cyclohexanedione according to the reported procedure for similar diketones was successful and the product **384** isolated in excellent yield (Scheme 132).[183]



Scheme 132. Reaction of nitroacrylate **231** with 1,3-cyclohexanedione

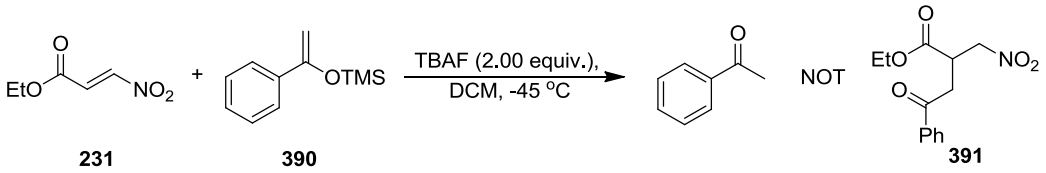
In light of the poor results from malononitrile, the use of an alternative reagent was investigated. Dimethylsulfonium dicyanomethylide **385**, can be synthesised easily from DMSO and malononitrile (Scheme 133)[184] and has been reported to react as a

soft nucleophile instead of the harder malononitrile anion.[185] Michael addition of ylide **386** on nitroacrylate **231**, should give zwitterion **387**, which after hydrolysis would afford nitroester **388**. However, when the reaction with this reagent was attempted in MeOH at rt, only starting material was observed. Heating the mixture to reflux overnight though gave none of the desired product **388** but only the unexpected nitroether **389** from 1,4-addition of methanol on nitroacrylate **231** (Scheme 133).



Scheme 133. Reaction of nitroacrylate **231** with ylide **385**

Silyl enol ethers, have been reported to perform conjugate additions on nitroalkenes in the presence of a fluoride source.[186] In light of this report, the reaction of 1-phenyl-1-trimethylsiloxyethylene **390** with nitroacrylate **231** in the presence of TBAF in DCM at -45 ^{o}C was investigated. However, only acetophenone and unknown degradation products were isolated and none of the desired 1,4-addition product **391** was observed (Scheme 134).

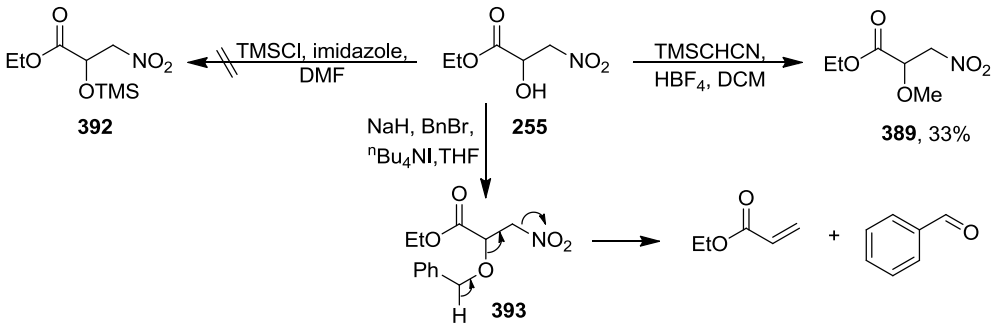


Scheme 134. Reaction of nitroacrylate **231** with **390**

2.5.2.2 Oxygen nucleophiles

The 1,4-additions of oxygen nucleophiles were then investigated. Initially, reaction of hydroxide anion with nitroacrylate **231** was attempted. Addition of a solution of nitroacrylate **231** in MeCN, to aqueous NaOH (0.10 M, 1.00 equiv.) cooled to 0 ^{o}C, mainly gave degradation products, with only 5% of the nitroalcohol **255** isolated. However, nitroalcohol **255** has been prepared previously by condensation of ethyl glyoxylate with nitromethane (62%, Scheme 85, section 2.3.1). It was thought that the

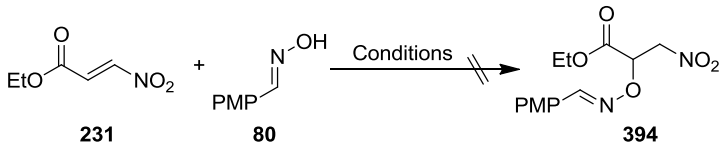
presence of a free hydroxyl group might interfere with the nitro-Mannich reaction, so it was attempted to protect the hydroxyl group. A few attempts were made to protect the hydroxyl group as a silyl ether **392**, benzyl ether **393** and methyl ether **389** (Scheme 135). Reaction of nitroalcohol **255** with TMSCl (1.20 equiv.) and imidazole (2.50 equiv.),[187] gave only a trace of **392** and 60% recovered starting material (Scheme 135). Reaction of nitroalcohol **255** with NaH (1.05 equiv.) and BnBr (2.00 equiv.) in THF, in the presence of $^{n}Bu_4N^{+}I^{-}$ (1.00 mol %),[188] after refluxing overnight, gave a complicated mixture of products, among which was benzaldehyde as well as traces of starting nitroalcohol and benzyl bromide. The presence of benzaldehyde indicates that the benzylated product **393** presumably eliminates HNO_2 to give ethyl acrylate which is volatile and evaporates (Scheme 135). Treatment of nitroalcohol **255** with methyl triflate (up to 9.00 equiv.) and proton sponge (5.00 equiv.) in $CHCl_3$ gave only 7% of the methylated product **389** after 22 h at reflux. Treatment with $TMSCHN_2$ (3.00 equiv.) and fluoroboric acid (1.00 equiv.) in DCM, at rt, for 1 h gave nitroether **389** in 33% yield (Scheme 135).[189]



Scheme 135. Attempts to protect nitroalcohol **255**

The enantioselective conjugate addition of oximes to trisubstituted *β*-nitroacrylates has been reported using a cinchona alkaloid as the chiral catalyst (Scheme 37, 1.2.3).[56] Specifically, oxime **80** derived from anisaldehyde was reported to give nitroesters **82** in good yield and *ee* (Scheme 136). This prompted us to investigate the 1,4-addition of oxime **80** to nitroacrylate **231** that would give a "masked" hydroxyl group in products **394**, which could be deprotected later in the synthesis. The deprotonation of oxime **80** with ^{n}BuLi and subsequent reaction with nitroacrylate **231** in THF, at -78 ^{o}C and then at rt gave only degradation products and unreacted oxime **80**, while simple reaction in toluene at rt with or without catalytic Et_3N (10.0 mol%)

was also ineffective. Use of quinine as the catalyst, in toluene, at 5 °C, as reported, gave only degradation.

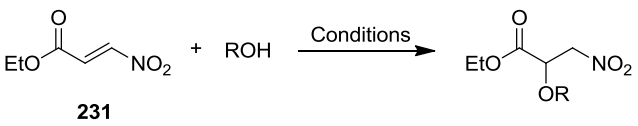


Scheme 136. Reaction of nitroacrylate **231** with oxime **80**

The reaction of nitroacrylate **231** with alkoxides was then investigated. Addition of a solution of MeONa in MeOH (0.10 M) to a solution of nitroacrylate at rt, gave only degradation of the starting material (baseline on TLC). This result was attributed to base-catalysed polymerisation of the starting material and as such it was attempted to reverse the addition mode. This was indeed beneficial, as it led to formation of the 1,4-addition product **389** in 62% yield, after quenching with AcOH and workup (H_2O/DCM extraction). Performing the same reaction at -78 °C gave **389** in an improved 80% yield. Furthermore, when investigating the reaction with ylide **385** before (Scheme 132, section 2.5.2.1), product **389** was isolated in 63% yield. Nitroacrylate **231** was refluxed in MeOH overnight and after 24 h **389** was isolated in 85% yield (Table 8).

Moreover, it was thought that acidic conditions could also affect the conjugate addition reaction of alcohols, by activation of the nitroalkene through protonation of the nitro group. However, the 1,4-addition of MeOH in acidic conditions was found to be ineffective. In view of the success of 1,4-addition after refluxing with neat alcohol as the solvent, this method was used for the synthesis of other derivatives (Table 8). Reaction with phenol was unsuccessful even at 70 °C (melted).

Table 8. Michael additions of alcohols to nitroacrylate **231**



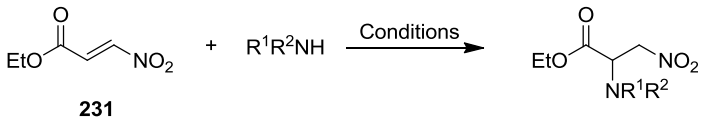
Entry	Nucleophile	Result	Product	Yield
1	MeONa/MeOH added to **231**, rt	Degradation	-	-
2	**231** added to MeONa/MeOH, rt	1,4-Addition	**389**	62%

3	**231** added to MeONa/MeOH, -78 ^{o}C	1,4-Addition	**389**	80%
4	MeOH/reflux	1,4-Addition	**389**	85%
5	EtOH/reflux	1,4-Addition	**395**	89%
6	BnOH/100 ^{o}C	1,4-Addition	**396**	62%
7	Phenol/Toluene	No reaction	-	-
8	Phenol/Toluene/reflux	No reaction	-	-
9	Phenol/Toluene/K_2CO_3 (30 mol %)	Degradation	-	-
10	Phenol/neat/melted (70^{o}C)	No reaction	-	-

2.5.2.3 Nitrogen nucleophiles

The 1,4-addition of nitrogen nucleophiles was subsequently investigated. The reactions were in most cases fast and without by-products, by simply mixing nitroacrylate **231** with the amine. With these conditions reactions with *para*-anisidine (1.80 equiv., 24 h), benzylamine (1.20 equiv., 1 h) and morpholine (1.10 equiv.) gave the desired products **397-399** in excellent yields (Table 9).

Table 9. Michael additions of amines to nitroacrylate **231**

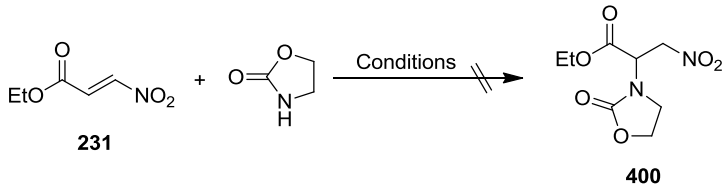


231

Entry	Nucleophile	Result	Product	Yield
1	*para*-anisidine	1,4-Addition	**397**	98%
2	Morpholine	1,4-Addition	**398**	98%
3	Benzylamine	1,4-Addition	**399**	81%

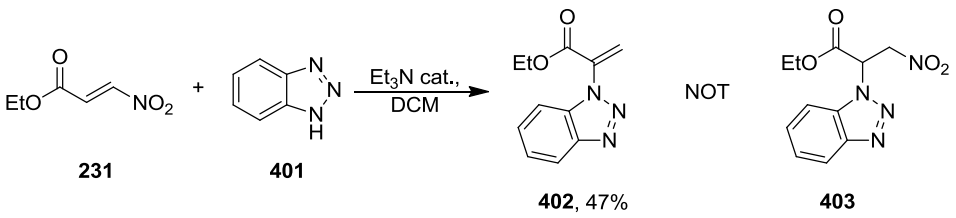
Reaction with other amines however was less successful. Reaction with hydrazine hydrate (1.00 equiv.) in MeOH, at rt gave complete consumption of the starting material after 24 h, but no 1,4-addition product was observed by ^{1}H NMR. The same result was observed with reaction with NH_3 (1.00 equiv., 0.5 M in THF) in THF at room temperature that led to complete degradation of the starting material in 5 min.

The conjugate addition of oxazolidin-2-ones to *β*-nitroalkenes after deprotonation with ^{t}BuOK and 18-crown-6, in THF, at 0 ^{o}C, has been reported (Scheme 39, section 1.2.4).[190] However, when this methodology was used with non-substituted oxazolidin-2-one at -78 ^{o}C, none of the desired 1,4-addition product **400** was observed, but only degradation of the starting material after 30 min of reaction (Scheme 137). Switching to a weaker catalytic base Et_3N (10.0 mol %), in THF at rt, gave a complex mixture of products. Use of a heterogenous base such as K_2CO_3 (30.0 mol%) unfortunately gave the same result.



Scheme 137. Michael addition of oxazolidinone to nitroacrylate **231**

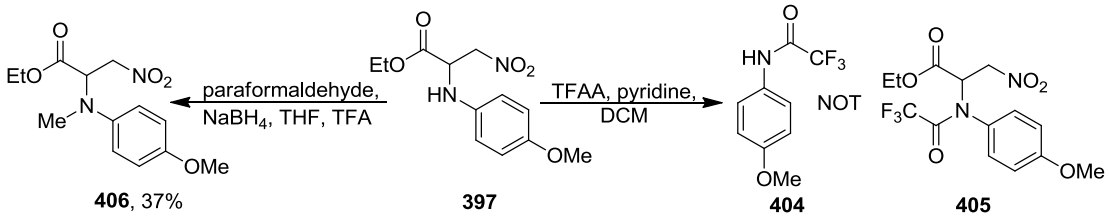
Furthermore, the reaction of nitroacrylate **231** with 1*H*-benzotriazole **401** (1.10 equiv.), in DCM was attempted. In the absence of base at rt, no reaction occurred, but in the presence of Et_3N (10 mol%) the starting material was consumed after 48 h. The only isolated product however was not the desired **402**, but the result of elimination of HNO_2 **403**, isolated in 47% yield (Scheme 138). This result is not unusual as elimination of HNO_2 from nitroalkanes under basic or acidic conditions has been reported,[191] while in this case this reaction is exacerbated by the presence of the acidic proton *α* to the ester group.



Scheme 138. Michael addition of 1*H*-benzotriazole to nitroacrylate **231**

In order to make more derivatives of 1,4-addition products, it was attempted to protect the free NH group of nitroamine **397**. It would be useful to know how various protecting groups would affect the reactivity of these nitroamines later on in the nitro-Mannich reaction. Moreover, the *para*-methoxyphenyl group could be removed to give a number of different derivatives.[116] Initially the protection of aniline **397** as a trifluoroacetamide was investigated, by reaction with TFAA (5.00 equiv.) and

pyridine (5.00 equiv.). From this reaction, though, only trifluoroacetamide **404** was isolated, indicating the elimination of the aniline. This was not unexpected as by forming a trifluoroacetamide, the aniline of **405** is turned into a good leaving group (Scheme 139). Protection with a silyl group was attempted but this was not effective even after using 12.0 equiv. of TMSCl, with Et_3N (1.00 equiv.) in DCM, at rt. Finally, it was attempted to methylate the nitrogen to give tertiary amine **406**. Treatment with MeI (4.50 equiv.) in refluxing acetone gave no products after 20 h,[192] but nitroamine **406** was successfully isolated (though in low yield) by a reductive amination reaction with paraformaldehyde (10.0 equiv.) and $NaBH_4$ (5.00 equiv.) in THF and TFA (Scheme 139).[193]



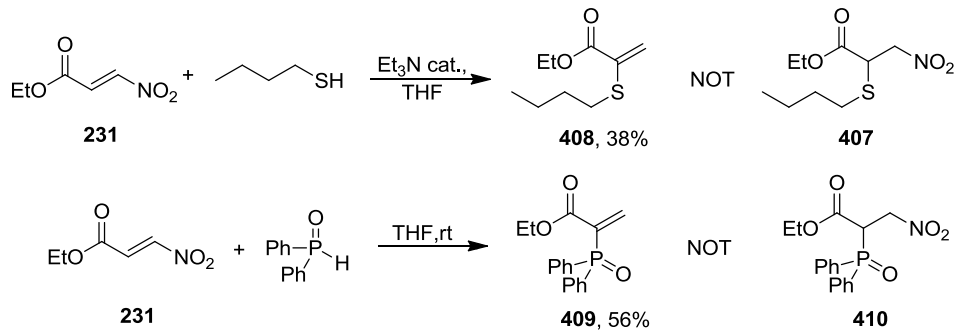
Scheme 139. Modifications of *para*-anisidine adduct **397**

2.5.2.4 Other nucleophiles

The conjugate addition of other nucleophiles to nitroacrylate **231** was also investigated. Reaction with 1-butanethiol (4.00 equiv.) and Et_3N (40 mol %), in THF, at rt, led to complete consumption of the nitroacrylate after 24 h. The only product isolated though, was not the desired **407** but **408** resulting from elimination of HNO_2 (Scheme 140). Repeating the same reaction in the absence of base, with 1-butanethiol (1.00 equiv.), in EtOH, at rt, was much faster (consumption of starting material in 10 min), but again failed to provide the desired product, as only a baseline spot was observed on TLC, indicating degradation presumably due to polymerisation.

The reaction with diphenylphosphine was then investigated. Simple addition of diphenylphosphine (1.10 equiv.) to a solution of **231** in THF, at rt, led to a complete consumption of the starting material in 20 min. It was not however possible to isolate any product, due to instability to purification. In light of this, it was considered that oxidation might be one reason for this instability, so it was decided to perform the reaction of nitroacrylate **231** with diphenylphosphine oxide. Reaction with diphenylphosphine oxide (1.10 equiv.) in THF, at rt, was slower than with

diphenylphosphine (completed in 17 h) and unfortunately the only product isolated was acrylate **409** and not **410** (Scheme 140).



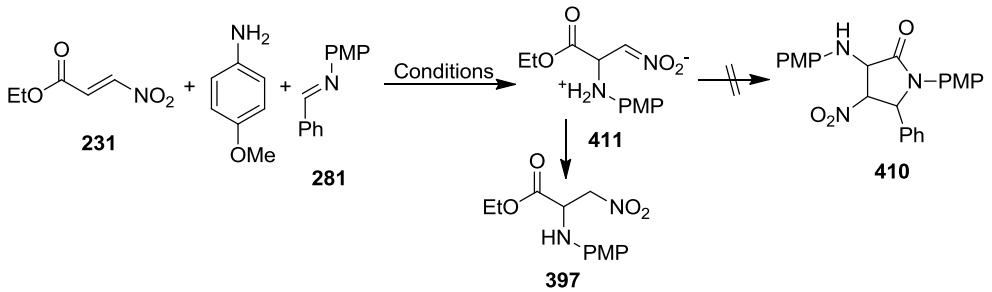
Scheme 140. Michael additions of 1-butanethiol and diphenylphosphine oxide to **231**

2.5.3 Nitro-Mannich reactions of 1,4-addition products of nitroacrylate 231

2.5.3.1 One-pot reactions

After investigating the conjugate additions of a variety of nucleophiles on nitroacrylate **231**, it was attempted to investigate whether a one-pot reaction would be effective. The conjugate addition to **231** in the presence of an imine and/or acid could yield either the nitro-Mannich product or the resulting lactamisation product.

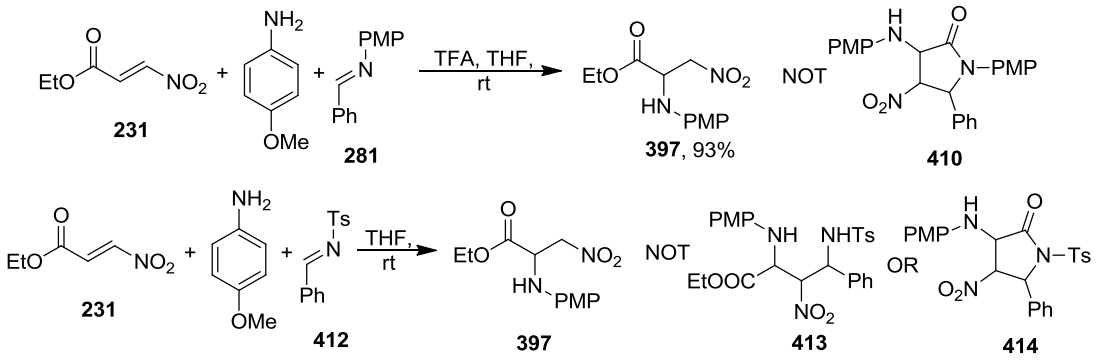
Initially, a one-pot reaction of nitroacrylate **231** with *para*-anisidine and imine **281** was explored. Reaction of nitroacrylate **231** with *para*-anisidine (1.20 equiv.) and imine **281** (2.00 equiv.) in toluene, at rt led to complete consumption of the nitroacrylate in 48 h and isolation of a single product, nitroamine **397** in 86% yield and none of pyrrolidinone **410** (Scheme 141). Switching to DCM, using 1.10 equiv. of *para*-anisidine and refluxing the mixture led to consumption of the nitroacrylate in 4 h and isolation of the nitroamine **397** in quantitative yield, but none of the desired nitro-Mannich product was isolated.



Scheme 141. Attempt of a one-pot 1,4-addition/nitro-Mannich/lactamisation reaction

These results were attributed to two possible reasons. The first, is that the nitronate anion **411** (Scheme 142) formed from the initial 1,4-addition reaction, tautomerises to **397** under the reaction conditions faster than it reacts with the imine. However, it is known from kinetic studies that protonation of nitronates to the nitroalkane can be slow.[194]

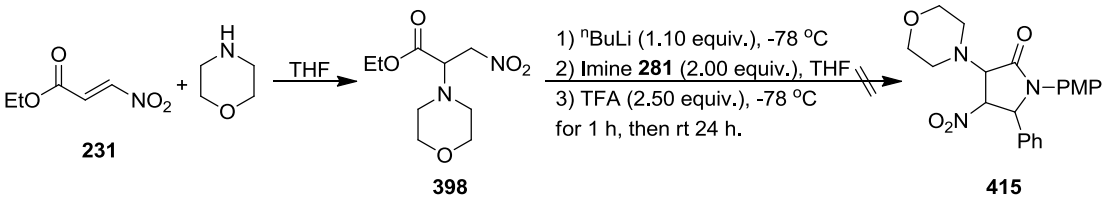
The second reason is that imine **281** is not reactive enough to participate in the nitro-Mannich reaction in the absence of acid, where it becomes protonated and hence more electrophilic. To test this hypothesis, the reaction of **231** with imine **281** (2.00 equiv.), *para*-anisidine (2.00 equiv.) and TFA (3.00 equiv.) in THF was investigated. The presence of acid is expected to protonate imine **281**, thereby making it more electrophilic. This reaction though, gave none of pyrrolidinone **410** but only the 1,4-addition product **397** after 48 h in 93% yield (Scheme 142). Furthermore, the reaction with the more electrophilic *N*-tosyl imine **412** was also attempted. Nitroacrylate **231** was reacted with imine **412** (1.50 equiv.) and *para*-anisidine (1.20 equiv.), in THF, at rt, in the absence of acid. These conditions however, gave none of nitroamine **413** or pyrrolidinone **414**, as only the starting materials and 1,4-addition product **397** were observed on TLC and ^{1}H NMR (Scheme 142). These two experiments suggest that the poor reactivity of the imine was not the reason that pyrrolidinone **410** was not formed in these conditions.



Scheme 142. Attempt of a one-pot 1,4-addition/nitro-Mannich/lactamisation reaction

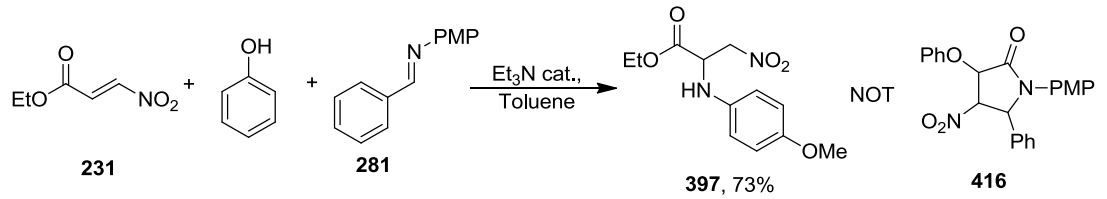
The tandem reaction of a few other nucleophiles was then investigated. Reaction of nitroacrylate **231** with morpholine (1.20 equiv.), imine **281** (1.50 equiv.) and TFA (2.00 equiv.) led after 24 h to consumption of the nitroacrylate, but only the 1,4-addition product of morpholine and unreacted imine **281** could be seen on TLC. A stepwise variant of the same reaction was also attempted. Nitroacrylate **231** and

morpholine (1.00 equiv.) were reacted first in THF, at rt (complete after 30 min, TLC) to give nitroamine **398**. The mixture was then cooled to -78 °C and a solution of ^{n}BuLi (1.10 equiv.) was added, followed by a solution of imine and then TFA. The reaction gave only a complicated mixture of products, but none of the desired pyrrolidinone **415** (Scheme 143).



Scheme 143. Attempt of a one-pot 1,4-addition/nitro-Mannich/lactamisation reaction

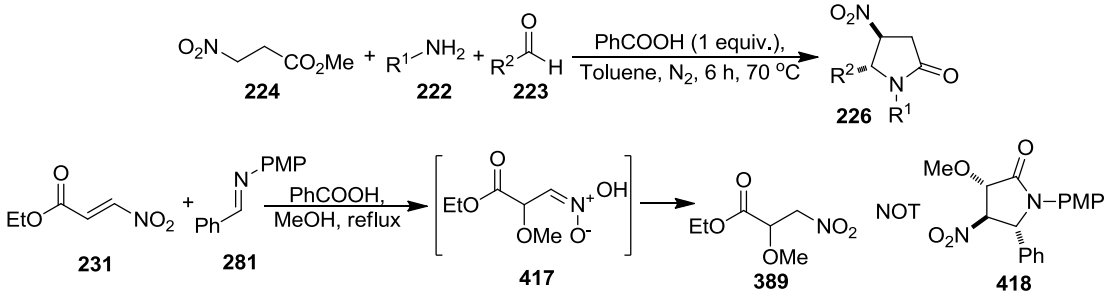
Attention was also given to the reactions with nucleophiles, where previously it was not possible to isolate the 1,4-addition product, such as with phenol and 1-butanethiol, hoping that a possible reactive 1,4-addition product could be intercepted by an imine which could then undergo lactamisation. Reaction of nitroacrylate **231** with 1-butanethiol (1.20 equiv.), imine **281** (2.00 equiv.) and Et_3N (30.0 mol %) led after 24 h to a complicated mixture of products with no pyrrolidinone detected. Reaction with phenol (1.50 equiv.) and imine **281** (1.50 equiv.), in toluene, at rt, in the absence of acid was very slow, while increasing the equivalents of phenol to 2.50, gave after 3 days only nitroamine **397** in 73% yield and none of pyrrolidinone **416** (Scheme 144). This indicates that the imine is presumably hydrolysed by water over time and the more reactive *para*-anisidine produced then reacts with the nitroacrylate **231**.



Scheme 144. Attempt of a one-pot 1,4-addition/nitro-Mannich/lactamisation reaction

The synthesis of pyrrolidinones **226** from refluxing nitroesters **224** with aldehydes **223**, amines **222** and benzoic acid has been reported (Scheme 76, section 1.5).[195] Inspired by this work, it was considered that refluxing a mixture of nitroacrylate **231**, imine **281** and benzoic acid in methanol might lead to the *in situ* formation of addition product **417**, which can potentially react with **281** and lactamise to the desired pyrrolidinone **418** (Scheme 145). However, when the reaction was performed with

1.50 equivalents of **281** and benzoic acid, only unreacted imine and the 1,4-addition product **389** were observed.

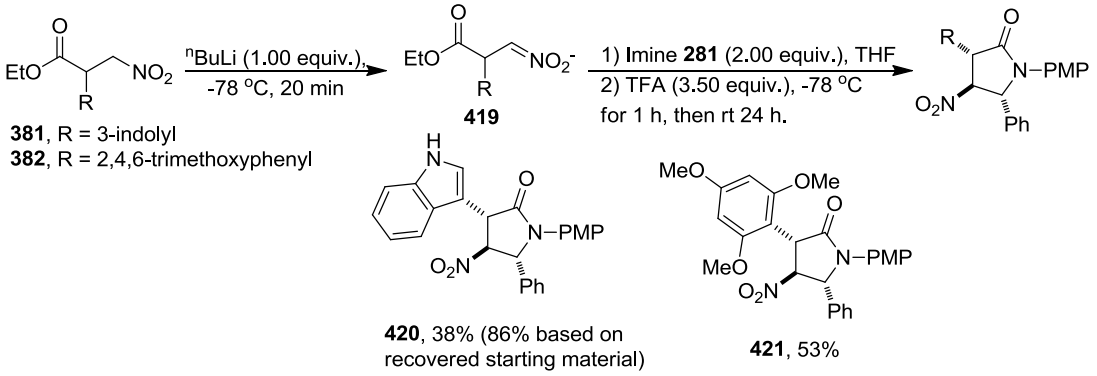


Scheme 145. Attempt of a one-pot reaction inspired by Dixons' methodology

2.5.3.2 Two-pot reactions

Due to the failure of the one-pot 1,4-addition/nitro-Mannich/lactamisation reaction, the two-pot procedure was investigated. In our general method, ^{n}BuLi was used to deprotonate the nitroalkanes α- to the nitro group to form nitronate **419**, followed by the procedure previously developed for the synthesis of pyrrolidinones **232** (addition of a solution of imine **281** followed by TFA).[116] This method has previously worked well for the synthesis of pyrrolidinone **279**, where the one pot reaction with diphenylzinc was unsuccessful (Section 2.3.3).

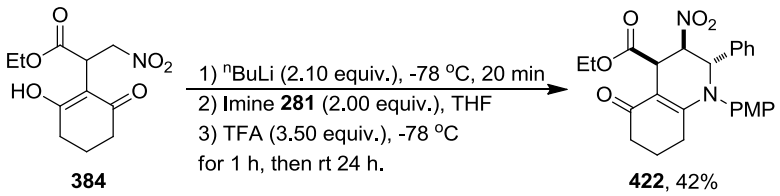
Initially the reactions of nitroalkanes derived from the conjugate addition of carbon nucleophiles were investigated. Reaction of nitroalkanes **381** and **382** gave the highly functionalised pyrrolidinones **420** and **421** respectively, in moderate yields as single diastereoisomers (Scheme 146).



Scheme 146. The nitro-Mannich/lactamisation reaction of adducts **420** and **421**

In the reaction of nitroalkane **384**, 2.10 equiv. of ^{n}BuLi were used, to account for deprotonation of the hydroxyl group. Interestingly this reaction gave

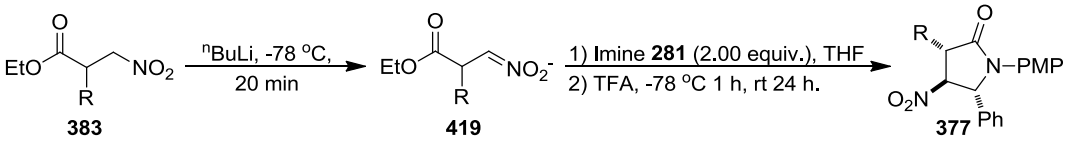
octahydroquinoline **422**, instead of the expected pyrrolidinone (Scheme 147). This result indicates that conjugate addition on the enone to form a six-membered ring is in this case preferential to lactamisation on the ethyl ester to form a five-membered ring.



Scheme 147. Synthesis of octahydroquinoline **422** from nitroalkane **384**

The nitro-Mannich reaction of the rest of the nitroalkane adducts was then investigated using the same procedure. The results, however, were not encouraging as in most cases the reactions led to degradation and when it was possible to isolate the pyrrolidinone products, they were found to be unstable both to chromatography and to storage (Table 10).

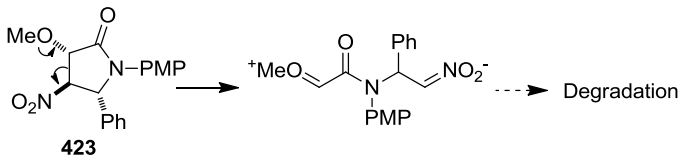
Table 10. Nitro-Mannich/lactamisation reactions of other Michael adducts



Entry	R group	^{n}BuLi/TFA (equiv.)	Product-Result/Yield
1	HO-	1.10/1.10[a]	**231**, imine and degradation
2	HO-	2.10/2.20	**231**, imine and degradation
3	MeO-	1.10/2.50	Expected **423**, 39%[b]
4	EtO-	1.10/2.50	Complicated
5	BnO-	1.10/2.50	Complicated
6	*p*-MeO-C_6H_4-NH-	1.05/2.10	**231**, imine and degradation
7	*p*-MeO-C_6H_4-NMe-	1.10/3.00	Complicated
8	Morpholine	1.10/2.20	Expected **424**, 7%[b]
9	BnNH-	1.10/2.00	Imine and degradation

[a]Reaction mixture was warmed to rt after the addition of ^{n}BuLi and recooled before the addition of the imine. [b]Product was found to be unstable.

It can be postulated that the desired pyrrolidinones are unstable due to the presence of an electron-rich group in the C^3 position of the pyrrolidinone. This could induce the ring opening of the pyrrolidinone that could lead to further degradation (Scheme 148).



Scheme 148. Degradation of pyrrolidinone **423**

2.5.3.3 Relative stereochemistry

Like the pyrrolidinones synthesised in sections 2.4 and 2.5, the pyrrolidinones obtained from our developed 2-pot procedure for non-zinc nucleophiles were isolated as single diastereoisomers. By comparison to the analogues synthesised before, the new analogues were tentatively assigned as bearing a *trans/trans* relative stereochemistry around the pyrrolidinone ring. It was not possible to obtain an X-ray crystal structure of any of these analogues, however the relative stereochemistry was assigned by comparison of their ^{1}H NMR coupling constants with the ones of previously synthesised pyrrolidinones. In our dialkylzinc methodology we reported couplings of 4.6-8.0 Hz for J_{HaHb} (Figure 21) and 3.4-6.3 Hz for J_{HbHc}. In the new analogues we reported couplings of 6.0-9.5 Hz for J_{HaHb} and 5.7-7.9 Hz for J_{HbHc} (Figure 21). Most J_{HaHb} values agree with our previous values, with the exception of trimethoxyphenyl analogue **421** which has a high value of 9.5 Hz, while values for J_{HbHc} are found to be slightly higher that the previously reported ones. Maybe the very hindered nature of the 2,4,6-trimethoxyphenyl substituent warps the conformation of pyrrolidinone **421**, but still leads to a coupling constant value within what could be expected for the depicted stereochemistry (Figure 21).

Molecular modelling for the four pyrrolidinones below,[128] predicts the dihedral angles H-C-C-H between H_a and H_b and between H_b and H_c to be in the range 161-165^o. This angle, according to the Karplus equation, corresponds to medium to high values for J_{HaHb} and J_{HbHc} as it was observed.[196]

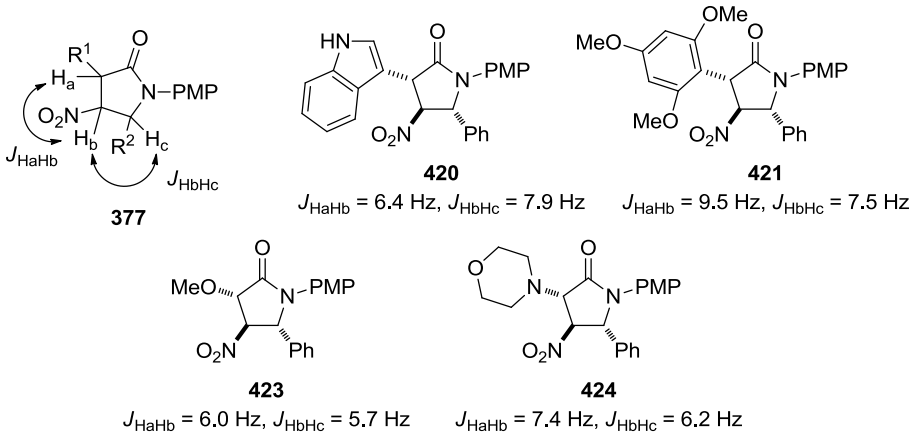


Figure 21

When investigating the nitro-Mannich reaction of 1,3-cyclohexadione adduct **384** earlier (Scheme 147), piperidine **422** was isolated as a single diastereoisomer. The relative stereochemistry of this piperidine was unknown. As shown in Figure 22, the observed values of coupling constants J_{HaHb} and J_{HbHc} were 5.3 and 8.7 Hz respectively (Figure 22). NOE studies have shown that irradiation of the C*H*COOEt (H_a) peak at δ 4.43 ppm caused a 3.17% and 0.57% enhancement for the protons H_b and H_c respectively (Figure 22). The medium value of J_{HaHb} suggests that the H_a-H_b is *cis*, while the larger J_{HaHb} suggests H_b-H_c are *trans*. The NOE values further support this hypothesis, as the very small enhancement of the peak of H_c excludes H_a and H_c being both axial, while the larger value for H_b suggests H_a and H_b have an axial-equatorial relationship. These data suggest a *cis/trans* relative stereochemistry and the most stable conformation to be the one shown below (Figure 22).

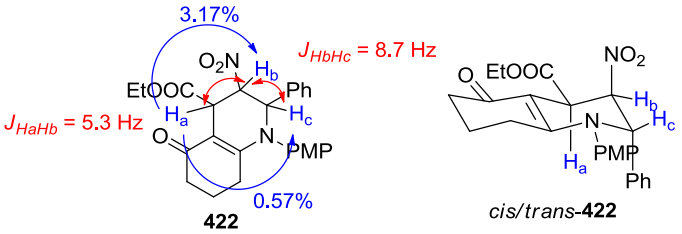
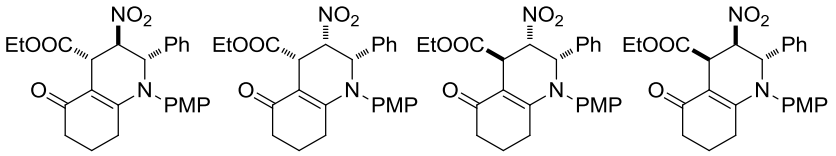


Figure 22

Molecular modelling was also used to confirm the relative stereochemistry of **422**.[128] All the possible diastereoisomers of **422** were modelled, in order to assess which one best fits the experimental data. After predicting the values of J_{HaHb} and J_{HbHc} and the distances of H_a-H_b and H_a-H_c (Table 11), it was concluded that the *cis/trans* stereochemistry is indeed the closest to the spectroscopic data. Deviation of 1.0 Hz in the calculated coupling constants is expected based on the error limit of the

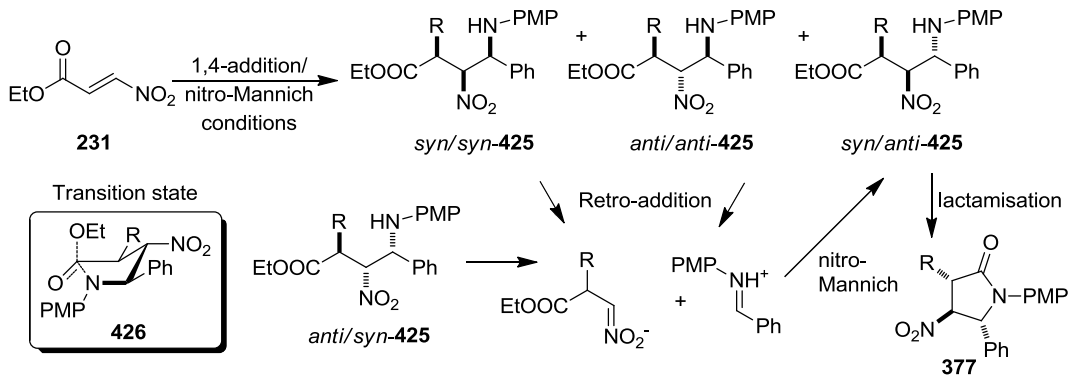
calculation. However, the higher deviation observed in this case can be attributed to contribution of other conformations to the experimental coupling constants, in particular the ring flipped conformation that would have the ester group axial and the nitro and phenyl groups equatorial.

Table 11. Predicted values of couplings J_{HaHb} and J_{HbHc} and the distances of H_a-H_b and H_a-H_c for the four possible diastereoisomers of **422**

Compound:				
Rel. ster.	*trans/trans*	*cis/cis*	*trans/cis*	*cis/trans*
J_{HaHb} (Hz)	11.8	3.9	12.1	4.5
J_{HbHc} (Hz)	10.6	2.0	3.4	10.6
H_a-H_b (Å)	3.09	2.41	3.08	3.06
H_a-H_c (Å)	2.64	2.45	3.84	3.84

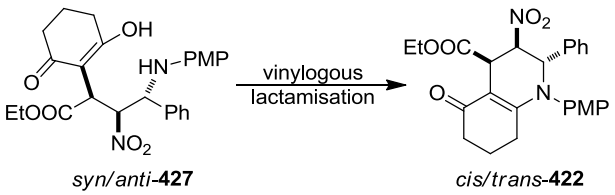
2.5.3.4 Source of diastereoselectivity

In previous work (section 2.3.8) with 1,4-addition of dialkylzinc reagents on nitroacrylate **231** followed by a nitro-Mannich reaction, it has been possible to isolate the intermediate *β*-nitroamines by protection as trifluoroacetamides **290**. However, in this work the intermediate *β*-nitroamines were not isolated, as they cyclised to give pyrrolidinones **377**. Since the ^{1}H NMR data support the *trans/trans* relative stereochemistry in the pyrrolidinone products, it can be postulated that only the *syn/anti*-**425** cyclises to give pyrrolidinones **377**, as it was observed before. It would be expected that the transition state **426** that gives the *trans/trans* pyrrolidinone would have the lowest energy, as it would have all the substituents in pseudo-equatorial positions, thereby minimizing 1,3-diaxial interactions (Scheme 149). Thereby it would be expected that all other *β*-nitroamine diastereoisomers equilibrate to *syn*/*anti*-**425**, which then cyslises (Scheme 149).



Scheme 149. Mechanism of the formation of pyrrolidinones **377**

Similarly, for piperidine **422** we have observed a *cis*/*trans* relative stereochemistry, which originates from cyclisation of the *syn/anti* *β*-nitroamine **427** (Scheme 150). In this case, the cyclisation that would give the presumably lowest energy diastereoisomer (*trans/trans*), *i.e.* the one having all substituents in an equatorial type arrangement, does not occur. It would appear that the *syn/anti*-**427** diastereoisomer was the major product from the reaction and only this product cyclises to piperidine **422**, whereas any other *β*-nitroamine diastereoisomers slowly degrade by retroaddition. Cyclisation is probably the rate determining step, therefore only the predominant *syn/anti* diastereoisomer cyclises and the other diastereoisomers degrade by retro-addition.



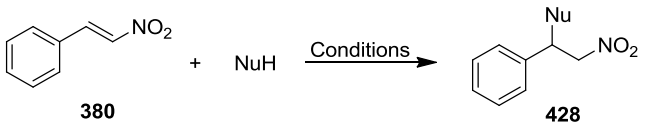
Scheme 150. Origin of *cis/trans*-**422**

2.5.4 Investigation of 1,4-addition reactions to *β*-nitrostyrene 380

2.5.4.1 Carbon nucleophiles

Continuing on with this work, it was then attempted to investigate the two-pot 1,4-addition/nitro-Mannich reaction to *β*-nitrostyrene **380** using the same range of nucleophiles. Initially, reactions with carbon nucleophiles were studied, that in most cases worked well to give the desired 1,4-addition products **428** in good yields (Table 12).

Table 12. Michael additions of carbon nucleophiles to *β*-nitrostyrene **380**

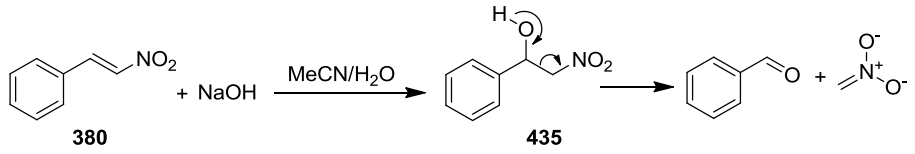


380 428

Entry	Nucleophile	Product-Result	Yield
1	Indole, $CeCl_3$, NaI, SiO_2	1,4-Addition, **429**	92%
2	1,3,5-trimethoxybenzene, $CeCl_3$, NaI, SiO_2	1,4-Addition, **430**	71%
3	Diethyl malonate, NaH, THF[182]	1,4-Addition, **431**	96%
4	Malononitrile, NaH, 15-crown-5, THF	No reaction	-
5	Malononitrile, DMF, proline[181]	1,4-Addition, **432**	89%
6	1,3-Cyclohexanedione, Et_3N, THF	Degradation	-
7	1,3-Cyclohexanedione, MeONa, MeOH[183]	1,4-Addition, **433**	34%
8	Meldrum's acid, Et_3N, DCM[197]	1,4-Addition, **434**	96%
9	1-phenylvinyl trimethylsilyl ether, THF, -45^{o}C, TBAF[186]	No product	-

2.5.4.2 Oxygen nucleophiles

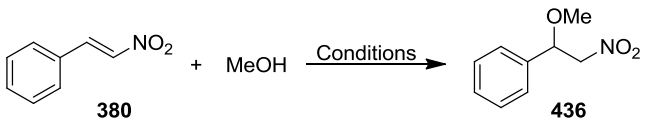
The formation of nitroalcohol **435** by conjugate addition of hydroxide to *β*-nitrostyrene was then investigated. When a solution of the nitroalkene in MeCN was added to an aqueous solution of NaOH (0.10 M, 1.00 equiv.) at 0 ^{o}C, the starting material was consumed in 5 min. The only product observed however, was benzaldehyde, which could be produced by elimination of nitromethane in the basic reaction conditions (Scheme 151). It was possible to synthesise nitroalcohol **435** in 50% yield, by a simple condensation of benzaldehyde with nitromethane in the presence of Et_3N as reported for other nitroalcohols.[115]



Scheme 151. Degradation of nitroalcohol **435**

The conjugate addition of alcohols/alkoxides to *β*-nitrostyrene **380**, was subsequently investigated. Even though this reaction is known,[198] it was decided to briefly screen a few possible methods in order to find the most effective one. We started this investigation with an optimisation of the reaction of **380** with methanol (Table 13). Interestingly, refluxing **380** in alcohol did not affect the 1,4-addition reaction (only nitrostyrene remained after 24 h reflux in MeOH). Attempts of an acid catalysed (entries 2 and 3) conjugate addition of MeOH were also unsuccessful. Reaction with MeONa however, gave the desired product **436**, the best result being from a modification of the reported procedure,[198] by performing the reaction exclusively in MeOH, at rt.

Table 13. Optimisation of the Michael addition of MeOH to *β*-nitrostyrene

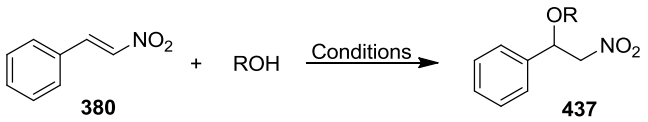


Entry	Nucleophile	Product-Result	Yield
1	MeOH, reflux, 22 h	No reaction	-
2	MeOH, TFA (10.0 equiv.), 21 h	No reaction	-
3	MeOH, H_2SO_4 (2.00 equiv.), 18 h	No reaction	-
4	MeONa, THF, 15-crown-5, 15 min	1,4-Addition	53%
5	MeONa, MeOH, Et_2O, 15 min[198]	1,4-Addition	62%
6	MeONa, MeOH, 15 min	1,4-Addition	73%

The optimised conditions were used with other alkoxides, using the alcohol of each alkoxide as the solvent (Table 14). This meant that with ^{t}BuOH the mixture had to be warmed to about 30 ^{o}C to remain liquid, which led to a poor yield of 1,4-addition

product. However, that could be improved if THF was used as a co-solvent (Table 14).

Table 14. Michael addition of alkoxides to *β*-nitrostyrene

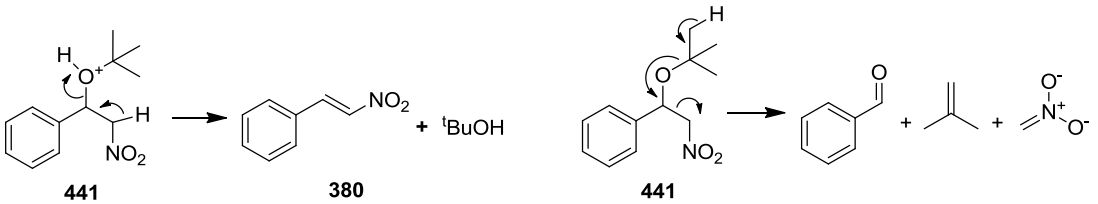


380 437

Entry	Nucleophile[a]	Product-Result	Yield
1	EtONa, EtOH	1,4-Addition, **438**	66%
2	BnONa, BnOH	1,4-Addition, **439**	66%
3	^{i}PrONa, ^{i}PrOH	1,4-Addition, **440**	58%
4	^{t}BuONa, ^{t}BuOH (30 ^{o}C)	1,4-Addition, **441**	9%
5	^{t}BuONa, ^{t}BuOH, DMF	Degradation[b]	-
6	^{t}BuOK, THF, 18-crown-6	Degradation[b]	-
7	^{t}BuONa (0.53 M in ^{t}BuOH), THF[c]	**380** and Benzaldehyde	-
8	^{t}BuONa (0.53 M in ^{t}BuOH), THF	1,4-Addition, **441**	40%

[a]Only 1.00 equiv. of alkoxide used in all cases. Reactions quenched with AcOH (6.00 equiv.). [b]Only baseline spot observed on TLC. [c]Reaction quenched with NH_4Cl.

In entry 7 (Table 15), although TLC indicated a complete consumption of starting material after quenching with NH_4Cl, only a trace of the desired 1,4-addition product **441** was observed, as well as a complicated mixture of degradation products, among which we could identify benzaldehyde and *β*-nitrostyrene. It is believed that nitroalkane **441** degrades to *β*-nitrostyrene by retro-1,4-addition upon workup (Scheme 152). The presence of benzaldehyde as the degradation product can be explained by elimination of 2-methylpropene and nitromethane (Scheme 152).



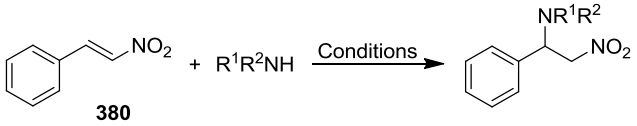
441 380 441

Scheme 152. Degradation of nitroalkane **441**

2.5.4.3 Nitrogen nucleophiles

The conjugate addition of amines to *β*-nitrostyrene was then investigated (Table 15). The electron rich 2,4-dimethoxyaniline gave a good yield of **442** by just stirring a mixture of the aniline (1.20 equiv.) with the nitroalkene, in DCM, at rt, for 19 h. This method though, was not effective for less electron rich anilines. In particular, stirring a solution of aniline (1.00 equiv.) with *β*-nitrostyrene in DCM, at rt, gave no product, while refluxing the reaction mixture gave incomplete consumption of the starting material. The same result was observed with *para*-nitroaniline (1.20 equiv.). A different methodology, performing the reaction in water, worked well for the 1,4-addition of aniline (Table 15).[199] The conjugate addition of *para*-nitroaniline was affected by deprotonation of the amine with ^{n}BuLi (1.00 equiv.) in THF, at -78 ^{o}C and subsequent addition of the nitroalkene, giving the 1,4-addition product **444** in medium yield.

Table 15. Michael addition of amines to *β*-nitrostyrene



380

Entry	Nucleophile	Product-Result	Yield
1	2,4-dimethoxyaniline/DCM	1,4-Addition, **442**	70%
2	Aniline/DCM	No reaction	-
3	Aniline/H_2O[199]	1,4-Addition, **443**	67%
4	*para*-nitroaniline/DCM	No reaction	-
5	*para*-nitroaniline/BuLi/THF	1,4-Addition, **444**	45%
6	Morpholine/DCM	1,4-Addition, **445**	22%
7	Morpholine/DCM/$Sm(OTf)_3$ cat.[200]	1,4-Addition, **445**	94%
8	$NH_2NH_2.H_2O$/MeOH	Degradation	-
9	NH_3/THF	Degradation	-
10	Benzotriazole/DCM[201]	1,4-Addition, **446**	83%
11	2-Oxazolidinone/THF/18-crown-6/^{t}BuOK[58]	1,4-Addition, **447**	90%

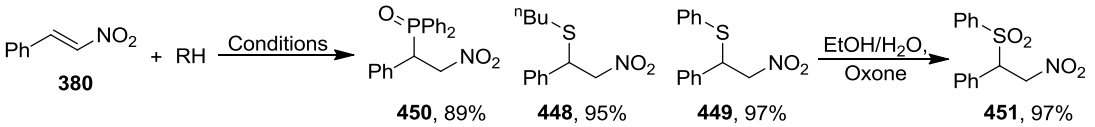
Reaction with morpholine (1.00 equiv.) in DCM, at rt, gave complete consumption of the nitroalkene in 24 h, but only a small yield of adduct **445** was isolated. Performing the reaction in the presence of Lewis acid $Sm(OTf)_3$ (0.200 mol%) led to a complete consumption of the nitroalkene in 24 h and isolation of adduct **445** in excellent yield (Table 16).[200]

Reaction of the nitroalkene with hydrazine (1.00 equiv.) in MeOH led to degradation, while reaction with a solution of NH_3 (5.00 equiv.) in THF gave no product after 5 h. Using a higher concentration of NH_3 by bubbling NH_3 gas through the solution for 5 min, led to degradation of the starting material after 1 h.

Reaction with benzotriazole (1.10 equiv.), in DCM, at rt, gave complete consumption of the nitroalkene in 19 h and isolation of adduct **446** in good yield. Reaction with oxazolidinone (1.00 equiv.), with ^{t}BuOK (1.00 equiv.) and 18-crown-6 (1.00 equiv.) in THF was over in 30 min and gave adduct **447** in excellent yield (Table 16).

2.5.4.4 Other nucleophiles

The conjugate addition of other nucleophiles to *β*-nitrostyrene was also investigated. Reaction with 1-butanethiol (1.00 equiv.) and Et_3N (5 mol %), in THF, at rt, led to complete consumption of **380** after 15 min and isolation of adduct **448** in excellent yield (Scheme 153). Using the same conditions, reaction with thiophenol gave adduct **449** in excellent yield after 15 min. Reaction with diphenylphosphine oxide (1.00 equiv.) in THF, at rt, was slower as the starting material was consumed in 24 h, but 1,4-addition product **450** was isolated in good yield (Scheme 153). Moreover, to broaden the scope of our 1,4-addition products, sulfide **449** was oxidised to sulfone **451** using oxone (1.50 equiv.) in MeOH and H_2O (Scheme 153).

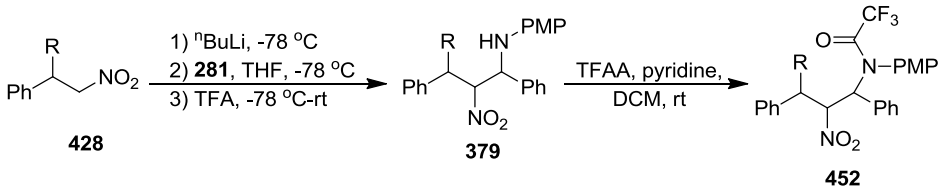


Scheme 153. Michael additions of other nucleophiles to *β*-nitrostyrene

2.5.5 Nitro-Mannich reactions of 1,4-addition products of *β*-nitrostyrene 380

With the 1,4-addition products **428** in hand, it was then attempted to perform the nitro-Mannich reaction from these. The procedure used was again deprotonation *α*- to the nitro group using ^{n}BuLi in THF at -78^{o}C, followed by addition of imine **281** (2.00

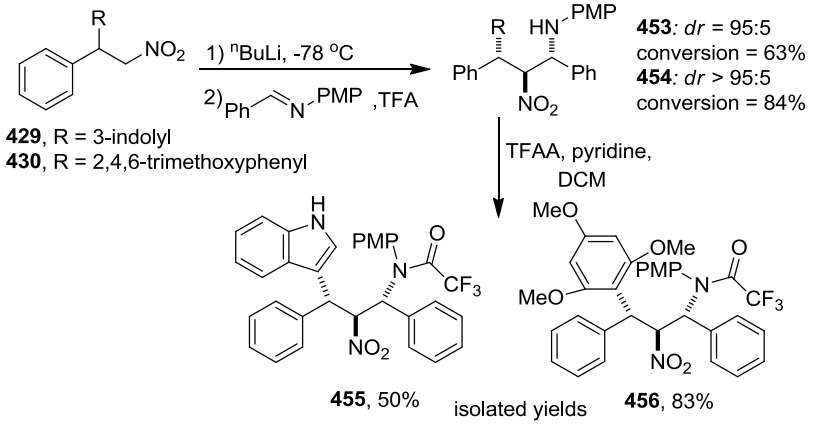
equiv.) and trifluoroacetic acid (3.50 equiv.), stirring for 1 h at this temperature and then warming to room temperature over 5 min and quenching with a solution of $NaHCO_3$.[35] The nitro-Mannich products **379** were unstable to purification and therefore were protected as trifluoroacetamides **452** with TFAA (3.00 equiv.) and pyridine (3.00 equiv.) in DCM, at rt (Scheme 154).



Scheme 154. The nitro-Mannich reaction of 1,4-addition products **428**.

2.5.5.1 Adducts of carbon nucleophiles

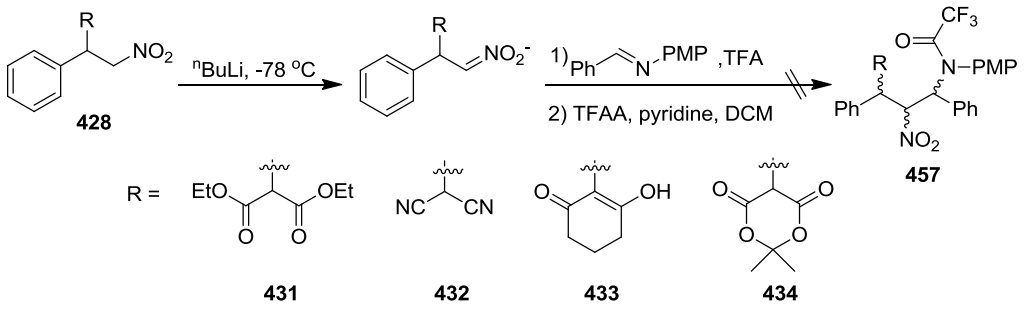
Initially the nitro-Mannich reactions of the adducts of carbon nucleophiles were investigated. Reaction of the two aromatic substituted nitroalkanes **429** and **430**, successfully gave the desired *β*-nitroamines **453** and **454**, isolated in good conversions (63% and 84% respectively) and excellent *dr* (Scheme 155). After protection, the resulting trifluoroacetamides **455** and **456** were isolated in good yields (Scheme 155), as single diastereoisomers bearing an *anti*/*anti* strereochemistry (section 2.5.6.1).



Scheme 155. Synthesis of trifluoroacetamides **455** and **456**

On the other hand, nitro-Mannich reaction of alkyl substituted nitroalkanes **431**-**434** was not successful and none of the desired trifluoroacetamides **457** could be isolated (Scheme 156). Reaction of malonate **431**, as well as malononitrile adduct **432**, gave only recovered starting material and unreacted imine. Cyclohexadione and Meldrum's acid adducts **433** and **434**, gave only a complicated mixture of degradation products.

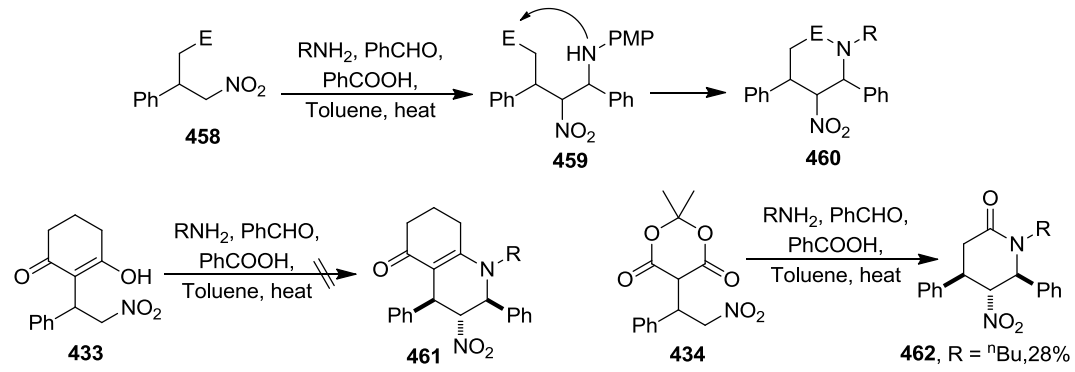
It is noted that 2.00 equivalents of ^{n}BuLi were used in those reactions as they all have another equally or more acidic proton than the one α to the nitro group.



Scheme 156. Nitro-Mannich reactions of other adducts of carbon nucleophiles

Due to the failure of the nitro-Mannich of the alkyl-substituted nitroalkanes above, it was attempted to use a different method to perform this reaction. It has recently been reported by Dixon, that by heating a mixture of a suitable nitroalkane, an amine and benzaldehyde with benzoic acid, in toluene, cyclisation occurs to give the desired piperidines.[195] Thereby we envisioned that a nitro-Mannich reaction of nitroalkane **458** bearing a suitable electrophilic group, with an amine and benzaldehyde would give β-nitroamine **459**, which under these reaction conditions should cyclise to form piperidinones **460** (Scheme 157). A similar reaction was observed before by the formation of piperidinone **422** from the nitro-Mannich reaction of cyclohexadione adduct **384** with imine **281** (section 2.5.3.2). The reactions of nitroalkanes **433** and **434** were investigated.

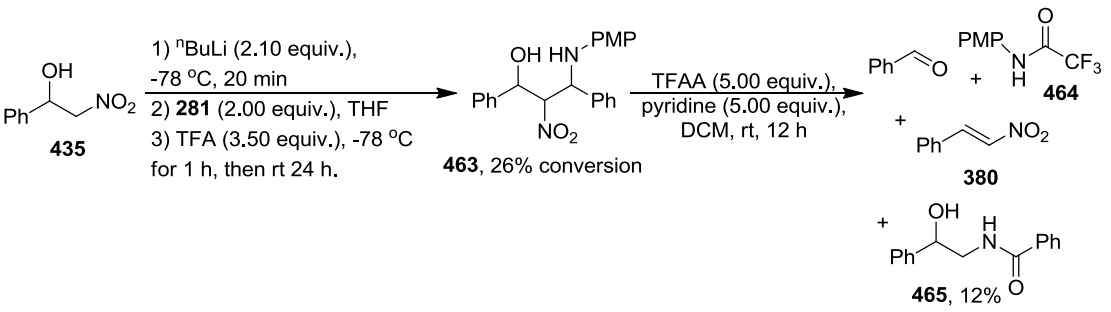
Starting from nitroether **433** and using the reported procedure,[195] amines benzylamine and ^{n}butylamine were tested, none of which gave the desirable product **461**, but only degradation (Scheme 157). Starting from nitroalkane **434**, three different amines were tested, *para*-anisidine, benzylamine and ^{n}butylamine. Only the reaction with ^{n}butylamine was successful and gave piperidinone **462** in 28% yield, resulting from a nitro-Mannich reaction, followed by loss of CO_2 and Me_2CO.



Scheme 157. Nitro-Mannich reactions using Dixons' methodology[195]

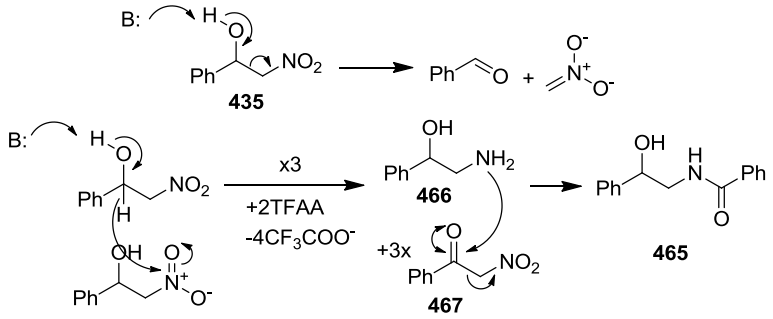
2.5.5.2 Adducts of oxygen nucleophiles

The nitro-Mannich reaction of nitroalcohol **435** was then investigated. Initial nitro-Mannich reaction, gave complete consumption of the starting nitroalcohol, to give what appeared by crude ^{1}H NMR to be the desired *β*-nitroamine **463** in 26% conversion, as well as unreacted imine **281** (70%) and traces of other products. Submitting the crude product to TFA-protection, gave benzaldehyde (40%), *β*-nitrostyrene (7%), the trifluoroacetamide of *para*-anisidine **464** (53%) and small amounts of other unknown products. After purification by column chromatography (Hexane:Me_2CO 8:2), unknown product **465** was isolated as a white solid (mp = 145-146 ^{o}C). This product had a molecular parent ion of m/z 242 Da from CI+ mass spectroscopy, with the high resolution mass supporting a molecular formula of $C_{15}H_{16}NO_2$. Two broad stretching bands in the IR spectrum at υ_{max} = 3410 and 3305 cm^{-1} supported the presence of OH and NH functionalities, as well as a carbonyl group with υ_{max}(C=O) = 1635 cm^{-1}. ^{1}H and ^{13}C NMR spectroscopy showed the presence of 10 aromatic protons, three aliphatic ones with a $CHCH_2$ structure and two exchangeable protons (OH and/or NH). The data were in agreement with that reported for amide **465**, which was isolated in only 12% yield from our reaction (Scheme 158).[202]



Scheme 158. Nitro-Mannich reaction of nitroalcohol **435**

The mechanism of the formation of amide **465** was intriguing. The amide nitrogen cannot originate from *para*-anisidine (present in imine **281**), as that would require the difficult removal of the *para*-methoxyphenyl group. We postulate it is more likely that the amide originates from the nitro group. This would require a reduction of the nitro group under the reaction conditions, which would require transfer of three hydrides to it from a reducing agent. Alternatively, this reduction could occur by single electron transfer, however that was not possible due to the absence of a suitable reagent in our conditions. In the speculative mechanism, nitroalcohol **435** can act as the reducing agent and transfer a hydride to the nitro group of another molecule of **435**, which can be made more favourable by acylation of the nitro group's oxygens by TFAA, reducing it eventually to amine **466**, giving nitroketone **467** as the by-product. Amine **466** can then react with **467** to give the observed amide **465** (Scheme 159). We have no evidence to support this mechanism as none of nitroketone **467** was observed in the crude reaction mixture, however this might be due to degradation.

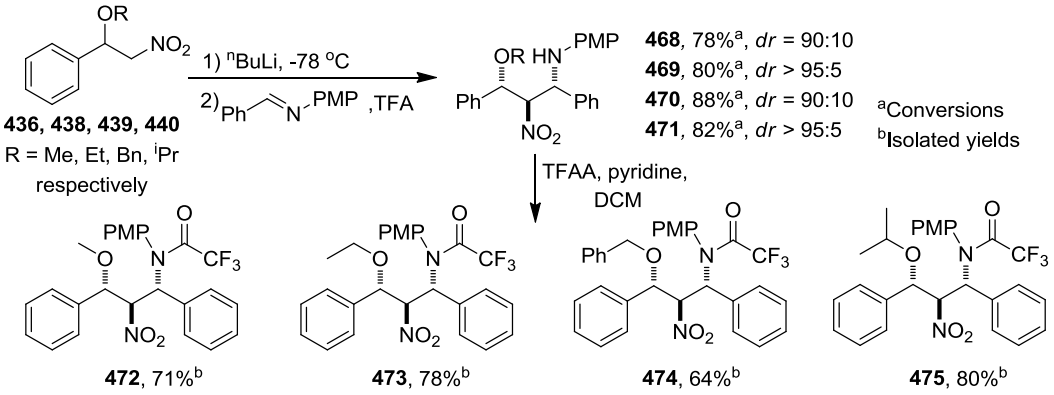


Scheme 159. Proposed mechanism for the formation of amide **465**

To our knowledge, the reduction of nitro groups from alcohols has only been reported once and only in the presence of palladium catalysis.[203] The reduction (transfer hydrogenation) of carbonyl groups from alcohols, is a lot more common and occurs in the presence of transition metals like Ruthenium,[204] trialkylaluminium compounds (Meerwein-Schmidt-Ponndorf-Verley reduction),[205] as well as enzymatic catalysis.[206] The transfer of hydride from nitroalcohols has not been observed before, however the transfer hydrogenation from benzyl alcohols in the presence of transition metals has been observed.[207] Various intermolecular redox reactions are widely known, such as the Cannizzaro reaction.[208]

The nitro-Mannich reactions of alcohol adducts **437**, using the general methodology, were generally succesfull and the desired *β*-nitroamines **468-471** were isolated in

good conversions and excellent diastereoselectivities (Scheme 160). After protection, the resulting trifluoroacetamides **472-475** were isolated in good yields as single diastereoisomers bearing again an *anti*/*anti* strereochemistry (section 2.5.6.2).



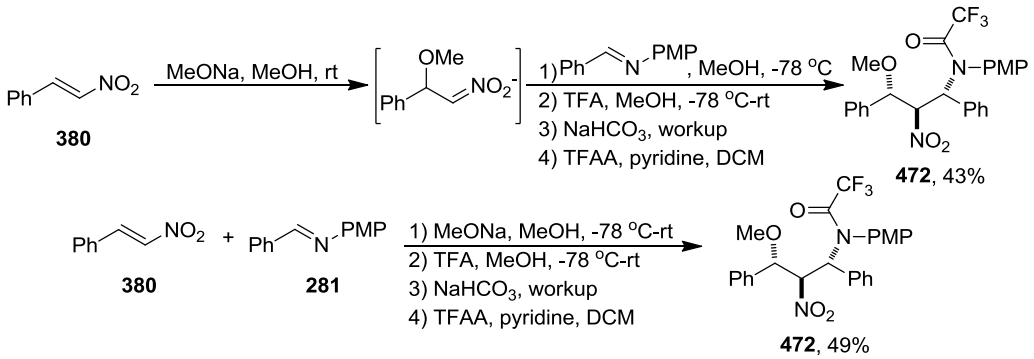
Scheme 160. Nitro-Mannich reactions of alcohol adducts to *β*-nitrostyrene

It is noted that in the case of ^{t}BuO-substituted nitroether **441** (Table 14, section 2.5.4.2), the nitro-Mannich reaction was very slow as mainly starting material was seen after 1 h at -78 ^{o}C. Extending the reaction time to 3 h at -78 ^{o}C led to complete consumption of the starting material, however only a trace of crude nitro-Mannich product was observed. Imine **281** (65% of the initial 2.00 equiv.), benzaldehyde (35% of the initial imine), *β*-nitrostyrene **380** (65% of the initial **441**) and ^{t}BuOH (80% of the initial **441**) were observed after workup. It is believed that nitroether **441** degrades to *β*-nitrostyrene and benzaldehyde in the same way observed during our efforts to synthesise **441** (section 2.5.4.2). However, this cannot be proven as in this case benzaldehyde is also forming from partial hydrolysis of the imine used.

Furthermore, it was attempted to perform the one pot 1,4-addition/nitro-Mannich reaction of methoxide to nitrostyrene. This would require the use of methanol as the solvent, as the 1,4-addition reaction of methoxide was found to be low yielding in other solvents. Methanol has not been used before as the solvent in the nitro-Mannich reaction, as it was incompatible to the previously used nucleophiles (dialkylzincs). Moreover, possible hydrogen-bonding of MeOH with the NH and NO_2 groups might interfere with the 6-membered transition state proposed for the nitro-Mannich reaction (section 2.5.6), thereby altering the selectivity of the reaction.

Reaction of *β*-nitrostyrene with MeONa in MeOH, followed by addition of the imine and TFA as solutions in MeOH and TFA-protection of the resulting *β*-nitroamines

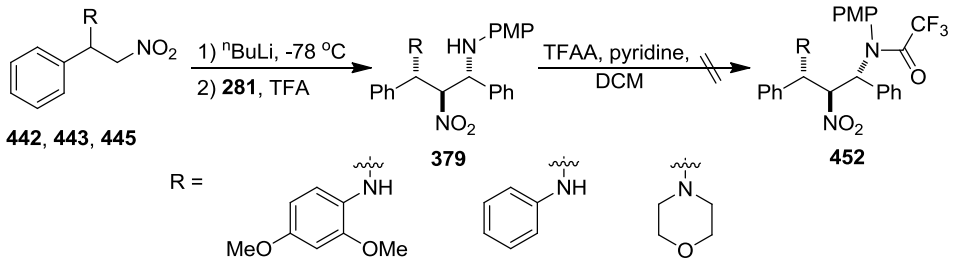
gave trifluoroacetamide **472** in 43% (Scheme 161). When imine **281** was present from the beginning as a mixture with the nitroalkene, trifluoroacetamide **472** was isolated in a yield of 49%, which is very close to the overall yield of the two-pot procedure (52%). This results show that the one-pot procedure in a solution of the alcohol, could potentially be used to substitute the two-step alkoxide conjugate addition/nitro-Mannich reaction protocol. A limitation of this one-pot procedure however, would be the melting point of the alcohol, as some heavier alcohols like benzyl alcohol would solidify at the initial temperature of the nitro-Mannich step (-78 °C).



Scheme 161. One-pot conjugate addition/nitro-Mannich reactions of *β*-nitrostyrene with MeONa

2.5.5.3 Adducts of nitrogen nucleophiles

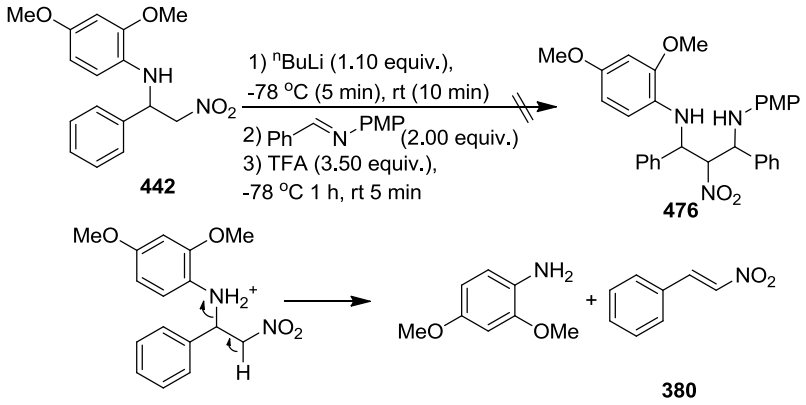
The nitro-Mannich reactions of *N*-substituted nitroalkanes were not as successful as those of the *O*-substituted ones. Electron rich amines **442**, **443** and **445** gave none of the desired trifluoroacetamides **452** (Scheme 162).



Scheme 162. Nitro-Mannich reactions of amine adducts to *β*-nitrostyrene

Nitro-Mannich reaction of 2,4-dimethoxyaniline adduct **442**, gave none of the desired *β*-nitroamine **476**, but instead an 88% conversion to *β*-nitrostyrene and 88% to 2,4-dimethoxyaniline and none of the initial **442** remained by ^{1}H NMR. It is postulated that the formation of *β*-nitrostyrene from the nitro-Mannich step might be attributed to

elimination of the aniline under the acidic reaction conditions (Scheme 163). In light of this result, it was attempted to reduce the equivalents of trifluoroacetic acid used from 3.50 to 1.00 equiv., however this gave the same result. Since there was no advantage to using 3.50 equiv. of TFA, it was decided to use 1.00 equiv. for the rest of our investigation into nitrogen adducts.



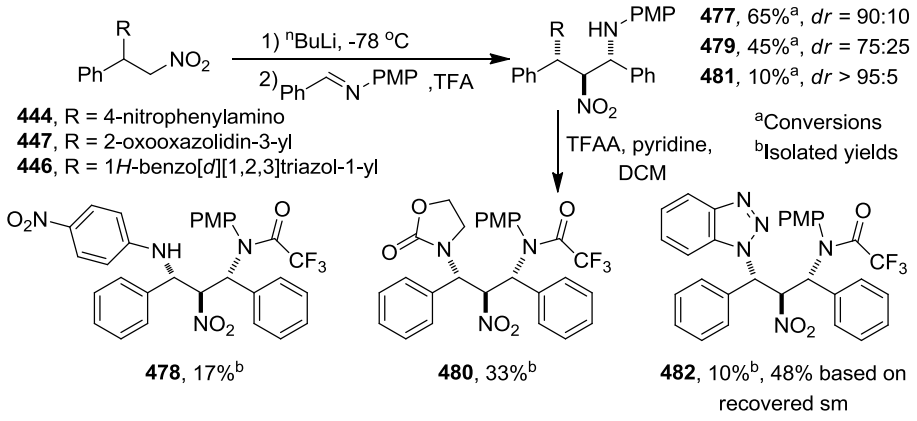
Scheme 163. Nitro-Mannich reaction of 2,4-dimethoxyaniline adduct **442**

Nitro-Mannich reaction of aniline **443**, gave a 32% conversion to the crude *β*-nitroamine and 28% to *β*-nitrostyrene. Attempts to TFA-protect the product led to decomposition and only benzaldehyde (from imine hydrolysis), and the trifluoroacetamides of aniline (53%) and *para*-anisidine (not isolated) were observed. Nitro-Mannich reaction of morpholine adduct **445** gave no desired *β*-nitroamine, but only starting material (43%) and *β*-nitrostyrene (24%).

In the case of *para*-nitroaniline as the substituent (**444**), the intermediate nitroamine **477** from the nitro-Mannich reaction was isolated in 65% conversion and a *dr* of 90:10 (Scheme 164). However, only a small yield of diastereomerically pure trifluoroacetamide **478** was isolated. This discrepancy between the conversion to nitroamine and yield of trifluoroacetamide indicated that a large amount of *β*-nitroamine **477** was degrading in the TFA-protection step. This degradation can be attributed tentatively to elimination of the trifluoroacetamide of any of the anilines in the basic reaction conditions. Attempts to synthesise trifluoroacetamide **478** in one pot from *β*-nitrostyrene were ineffective, as only a trace of the intermediate **477** was observed by ^{1}H NMR.

Trifluoroacetamide products were also isolated from the reactions of oxazolidinone **447** and benzotriazole **446**. In the case of **447** the intermediate nitroamine **479** was

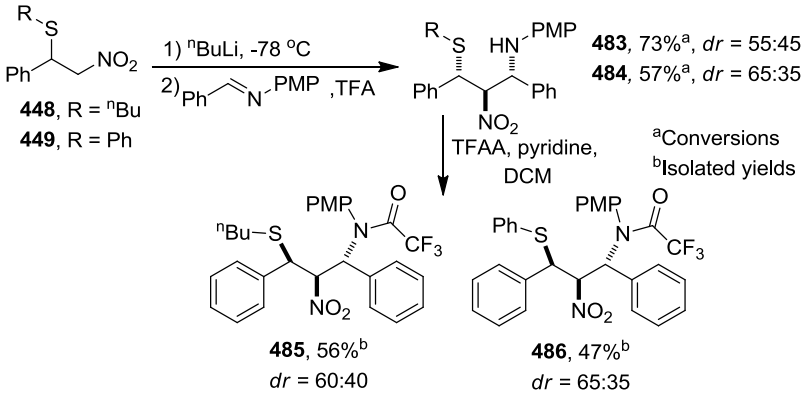
isolated in modest conversion and *dr* and only a small yield of diastereomerically pure trifluoroacetamide **480** was isolated. With benzotriazole adduct **481**, a small yield of trifluoroacetamide **482** was isolated, with a 79% yield of recovered starting material. The three products were assigned as having an *anti*/*anti* configuration (section 2.5.6.3).



Scheme 164. Nitro-Mannich reactions of amine adducts to *β*-nitrostyrene

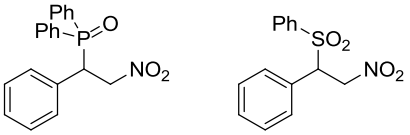
2.5.5.4 Adducts of other nucleophiles

Finally, the nitro-Mannich reaction of sulfur and phosphorus adducts was investigated. Reaction of ^{n}butyl sulfide **448** gave unreacted sulfide (14%) and crude *β*-nitroamine **483** in a 73% conversion and *dr* of 45:55, while phenyl sulfide **449** gave unreacted sulfide (14%) and crude *β*-nitroamine **484** in 57% conversion and *dr* of 65:35. Subsequent TFA-protection, led to isolation of the desired trifluoroacetamides **485** and **486** in medium yields and almost unchanged *dr* (Scheme 165). The major products were assigned as the *syn/anti* diastereoisomers (see section 2.5.6.5).



Scheme 165. Nitro-Mannich reactions of thiol adducts to *β*-nitrostyrene

Reactions of sulfone **451** and phosphine oxide **450** (Figure 23), were however less successful. Nitro-Mannich reaction of sulfone **451** gave only recovered starting material and unreacted imine, as did reaction of **450** (Figure 23). A reason for this lack of reactivity could be the possible deprotonation α to the phosphorus or sulfur atom, instead of α to the nitro group. The pka's in DMSO are expected to be ≈25 for the proton α to the phosphorus, ≈24 for the one α to the sulfone, and ≈17 for the one α to the nitro group, based on literature values of related compounds.[209] Therefore it is unlikely that deprotonation would occur α to the phosphorus or sulfur atom. To our knowledge, there is only one example of a conjugate addition of a β-nitrophosphate[210] and one for a β-nitrosulfone,[211] and in both reports the conjugate addition occurred α to the nitro group. Moreover, the electron withdrawing phosphine oxide and sulfone groups would be expected to make the nitronate anion less nucleophilic, thereby unreactive in the nitro-Mannich reaction.



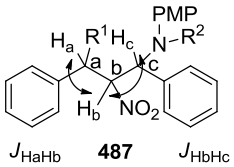
450 **451**

Figure 23

2.5.6 Relative stereochemistry

As previously described, the trifluoroacetamides synthesised by our two pot 1,4-addition/nitro-Mannich methodology, were isolated mostly as single diastereoisomers, with the exception of sulfides **485** and **486** (60:40 and 65:35 *dr*). To prove the relative stereochemistry, some trifluoroacetamides were crystallized and X-ray diffraction crystal structures were obtained. All crystal structures showed an *anti/anti* relative stereochemistry. However, it was not possible to obtain crystal structures for all analogues. Therefore, it was attempted to assign the relative stereochemistry for the rest of the trifluoroacetamides, by comparison of their ^{1}H NMR coupling constants with the analogues where the stereochemistry was confirmed by X-ray crystallography. For this assignment we used the coupling constants between the 1,4-addition centre and the nitro group (J_{HaHb}) and between the nitro group and the amino centre (J_{HbHc}) of our derivatives **487** (Table 17).

Table 17. Table of coupling constants of synthesised *β*-nitroamines and trifluoroacetamides



R^1	R^2 = H		R^2 = TFA	
	J_{HaHb} (Hz)	J_{HbHc} (Hz)	J_{HaHb} (Hz)	J_{HbHc} (Hz)
C	11.5-12.2	3.4	6.7-11.5	6.8-9.2
O	8.8-9.3	5.3-6.2	6.7-8.5	10.7-11.0
N	9.1	6.2	9.9-10.7[a]	6.3-7.9[a]
S	9.4-11.0[b]	3.5-5.3[b]	5.1-6.2[b,c]	9.8-10.4[b,c]

[a]The values for *para*-nitroaniline analogue are omitted.

[b]Values for the major diastereoisomer.

[c]All other trifluoroacetamides were isolated as single diastereoisomers.

As it can be seen in Table 17, although within each group of compounds the coupling constants generally fall within a narrow range (<2 Hz), there are significant differences between some groups, so it was decided to treat them separately. In previous work it had been proposed that *β*-nitroamines can exist in a chair conformation, due to hydrogen bonding between the NH proton and the nitro group (Figure 24).[114] In this chair conformation, we expect the *anti*-*β*-nitroamines to have proton H_b in an axial position and H_c in an equatorial one. This means that the dihedral angle between them would be ≈60 °, which should have a medium coupling constant according to Karplus equation, as it was indeed observed for J_{HbHc}.

After TFA-protection of the nitroamines, no intramolecular hydrogen bonding is possible (with the exception of aniline **478**) and the molecule would have an open chain conformation. It is assumed however, that the molecule would have a conformation bearing the two electron withdrawing groups on opposite sites, in order to reduce the overall dipole moment (Figure 24). This would mean a dihedral angle of 180°, which would have a larger coupling constant for J_{HbHc}, which can be observed for all our analogues.

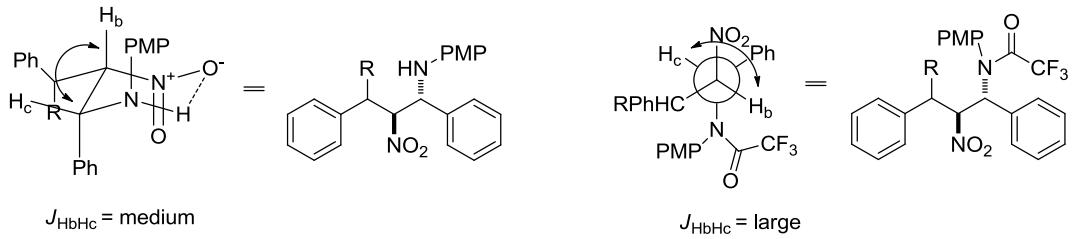


Figure 24. Explanation of the observed coupling constants

The assignment of the remaining centre (H_a-H_b) though was more intriguing. In the *β*-nitroamines (R^2 = H) it is expected that the molecule would reside in a conformation where the substituents of the exocyclic carbon and the endocyclic one would be staggered (Figure 25). Moreover, H_a is expected to occupy mostly the position antiperiplanar to H_b, in order to minimize any *pseudo*-diaxial interactions with the axial phenyl group (Figure 25). If the R group is electron withdrawing, it is expected that it would prefer to be antiperiplanar to the nitro group so as to minimize the dipole of the molecule. This would mean a dihedral angle of 180° between H_a and H_b, which would give a larger coupling constant for J_{HaHb}, as was observed for all our analogues.

After TFA-protection of the nitroamines, the molecule would have an open chain conformation, so again the Newman projections of the same two carbons must be considered. With the same reasoning as before, if the R group is electron withdrawing it is believed that the molecule would have a conformation bearing R antiperiplanar to the nitro group, so as to reduce the overall dipole (Figure 25). This would mean a dihedral angle of 180 ° between H_a and H_b, which would lead to a large coupling constant for J_{HaHb}. This was observed for most analogues with the exception of the two sulfides **485** and **486**.

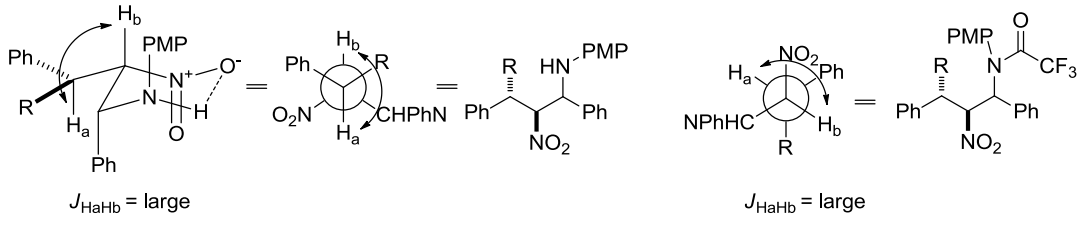


Figure 25. Explanation of the observed coupling constants

2.5.6.1 Carbon adducts

Trifluoroacetamides **455** and **456** were isolated from the 1,4-addition of carbon nucleophiles followed by a nitro-Mannich/TFA-protection reaction. Fortunately, it

was possible to obtain an X-ray crystal structure of trimethoxyphenyl analogue **456**, which showed an *anti/anti* relative stereochemistry (Figure 26).

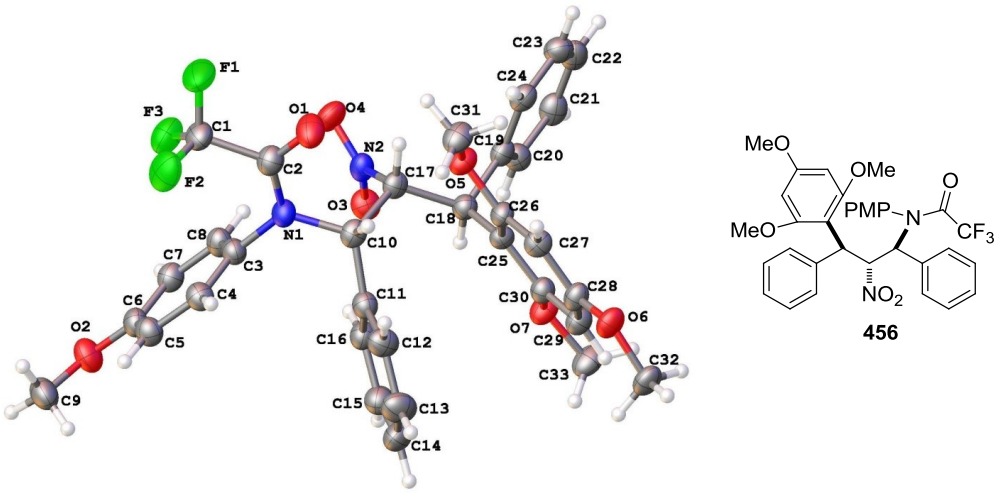


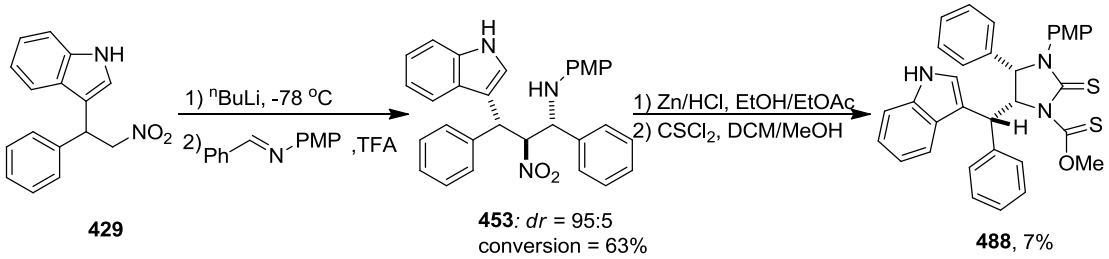
Figure 26. X-ray crystal structure of (±)-**456**

With indole analogue **455**, it was not possible to obtain a crystal structure as the compound was not crystalline, thus a comparison of the coupling constants J_{HaHb} and J_{HbHc} with those of trimethoxyphenyl analogue **456** was attempted. When examining the values for the two crude *β*-nitroamines **453** and **454**, it was observed that for the trimethoxyphenyl adduct **454**, J_{HaHb} was 12.2 Hz and J_{HbHc} could not be distinguished, whereas for indole adduct **453**, J_{HaHb} = 11.5 Hz and J_{HbHc} = 3.4 Hz. As the values for J_{HaHb} are equally large, the two compounds are expected to have the same *anti* relationship between H_a and H_b (Table 17). In light of the absence of data for J_{HbHc} though, the remaining H_b-H_c relative stereochemistry could not be determined.

The coupling constant data for the respective trifluoroacetamides were not as helpful, as for **456**, J_{HaHb} = 11.5 Hz and J_{HbHc} = 3.4 Hz, while for **455**, J_{HaHb} = 6.7 Hz and J_{HbHc} = 9.2 Hz were measured. It is not safe to draw any conclusions from the values of coupling constants of trifluoroacetamides **455** and **456**, as those are the result of averaging the coupling constants of all the possible conformations, due to free rotation along the C-C bonds between our stereocentres.

In order to assign the H_b-H_c relative stereochemistry of indole **455**, it was decided to perform another experiment. After the nitro-Mannich reaction of indole **429**, the produced *β*-nitroamine **453** was subjected to reduction of the nitro group with Zn/HCl. The crude diamine then produced, was reacted with thiophosgene in

DCM/MeOH, to give imidazolidine-2-thione **488** as a single diastereoisomer (Scheme 166). The product was isolated in low yield, presumably due to degradation of part of the *β*-nitroamine **453** in the reduction conditions and other side reactions in the cyclisation step. The reaction conditions were not optimised due to time constrains, however some useful information could be obtained from derivative **488**, which presumably comes from the major diastereoisomer of the initial nitroamine **453**.



Scheme 166. Synthesis of imidazolidine-2-thione **488**

NOE studies have shown that irradiation of the H_b peak at δ 6.16 ppm caused a 3.95% enhancement of the peak of H_c, but only 0.70% of H_a (Figure 27). The big value for H_c indicates that the relative stereochemistry between H_b and H_c in the imidazolidine-2-thione ring is *cis*, which corresponds to an *anti* configuration between the nitro group and the amine in *β*-nitroamine **453**. The small value of H_a can be explained by a possible *anti* conformation in the Newman projection between protons H_a and H_b (Figure 27). The *anti* positioning of these two protons was also supported by the large value of the coupling constant between them of 10.3 Hz.

Furthermore, imidazolidine-2-thiones like **488** have been reported by the Anderson group as a means of protecting 1,2-diamines.[14] In particular, imidazolidine-2-thione **489** which was isolated in enantiomerically pure form and characterised by X-ray crystallography, greatly resembles our derivative **488**.[212] Therefore, it was possible to compare, at least for the stereochemistry of the imidazolidine ring, the coupling constants for the coupling H_b-H_c (J_{HbHc}). The value reported for **489** was 9.2 Hz which is very close to the one observed in **488** that was 8.7 Hz, further confirming the above conclusion.

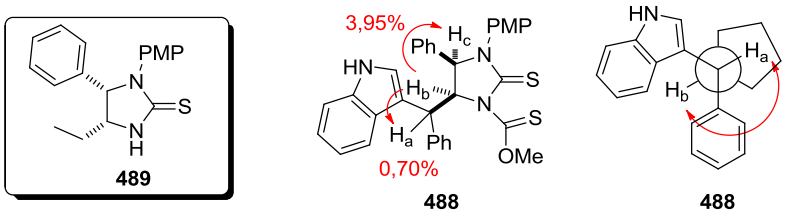


Figure 27

As further proof, molecular modelling was used to predict the values of J_{HaHb} and J_{HbHc} for β-nitroamine **453**, trifluoroacetamide **455** and imidazolidine-2-thione **488**.[128] The values were in agreement with our experimental data for both the β-nitroamine **453** and imidazolidine-2-thione **488** (Table 18). Based on these results, the relative stereochemistry of trifluoroacetamide **455** can be tentatively assigned as being *anti/anti*.

Table 18. Predicted and experimental values of coupling constants of **453**, **455** and **488**

Compound	***J* observed (Hz)**		***J* predicted (Hz)**	
	J_{HaHb}	J_{HbHc}	J_{HaHb}	J_{HbHc}
453	11.5	3.4	11.4	2.8
455	6.7	9.2	11.4	10.2
488	10.3	8.7	11.1	6.9

When investigating the nitro-Mannich/cyclisation reaction of Meldrum's acid adduct **433** with ^{n}butylamine and benzaldehyde, piperidinone **462** was isolated (Section 2.5.5.1, Scheme 157). The observed coupling constant values of this compound were 11.3 and 8.6 Hz for J_{HaHb} and J_{HbHc} respectively (Figure 28). By comparison of the coupling constants with the very similar reported piperidinone **490**, compound **462** can be tentatively assigned as having a *trans/trans* relative stereochemistry around the piperidinone ring (Figure 28).

NOE studies have shown that irradiation of the C*H*CH$_2$ peak (H$_c$) at δ 3.73 ppm caused a 0.37% enhancement for protons H$_b$ and 1.83% for proton H$_a$ (Figure 28). These values were in agreement with a *trans/trans* relative stereochemistry where the three protons H$_a$, H$_b$ and H$_c$ are in axial positions, therefore H$_a$ is close in space to H$_c$.

Furthermore, molecular modelling of *trans/trans*-**462** predicted the values of J_{HaHb} and J_{HbHc} to be 11.3 and 10.6 Hz respectively, values that are very close to our experimental data.[128] The distances H_a-H_c and H_b-H_c were also calculated for *trans/trans*-**462** and found to be 2.45 and 3.07 Å respectively, which agrees with our observed NOE values.

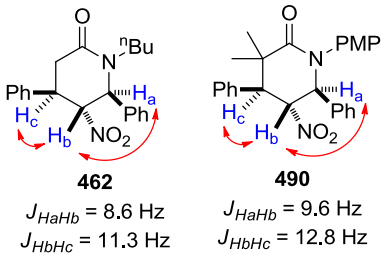


Figure 28

2.5.6.2 Oxygen adducts

From the nitro-Mannich reaction of oxygen adducts of *β*-nitrostyrene, trifluoroacetamides **472-475** were obtained. All the analogues of this series show a close range of coupling constants. For the intermediate *β*-nitroamines **468-471**, a medium value of 5.3-6.2 Hz was observed for J_{HbHc} and a larger value of 8.8-9.3 Hz for J_{HaHb}, as expected. For the trifluoroacetamide products the value for J_{HaHb} decreased slightly to 6.7-8.5 Hz and that of J_{HbHc} increased to 10.7-11.0 Hz. An X-ray crystal structure was obtained for methoxy-substituted analogue **472**, which showed an *anti/anti* relative stereochemistry (Figure 29). Due to the close resemblance of the coupling constant values of all the analogues, they can all be comfortably assigned as the *anti/anti* diastereoisomers.

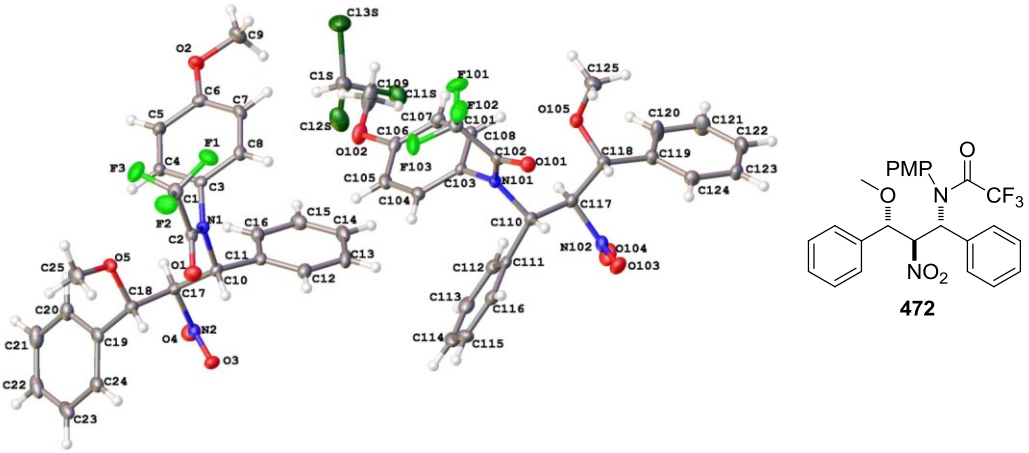


Figure 29. X-ray crystal structure of (±)-**472**

2.5.6.3 Nitrogen adducts

It was then attempted to assign the relative stereochemistry of trifluoroacetamides **478**, **480** and **482**, derived form nitrogen adducts to *β*-nitrostyrene. Unfortunately, some of the coupling constants of *β*-nitroamines **479** and **481** (appendix 1) could not be distinguished from the ^{1}H NMR spectra. Although the values for **477** could be measured, this nitroamine has two NH protons, therefore it is unknown which one would hydrogen bond to the nitro group to give a chair conformation.

When looking at the coupling constant values for the three trifluoroacetamides, it can be seen that **480** and **482** have a large value for J_{HaHb} (9.9-10.7 Hz), while J_{HbHc} has a slightly smaller one (6.3-7.9 Hz). The coupling constant values for *para*-nitroamine analogue **477** were significantly different, which is explained below. An X-ray crystal structure was obtained for trifluoroacetamides **480** and **482,** showing an *anti/anti* relative stereochemistry in both cases (Figure 30).

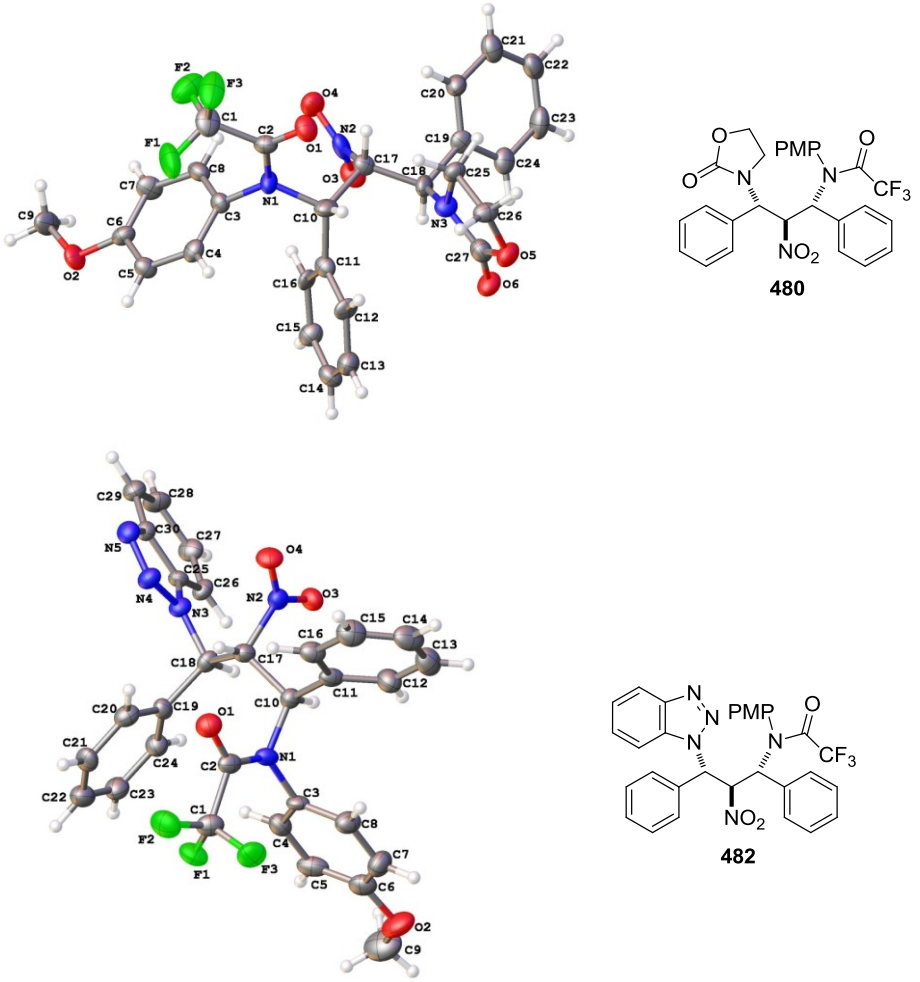
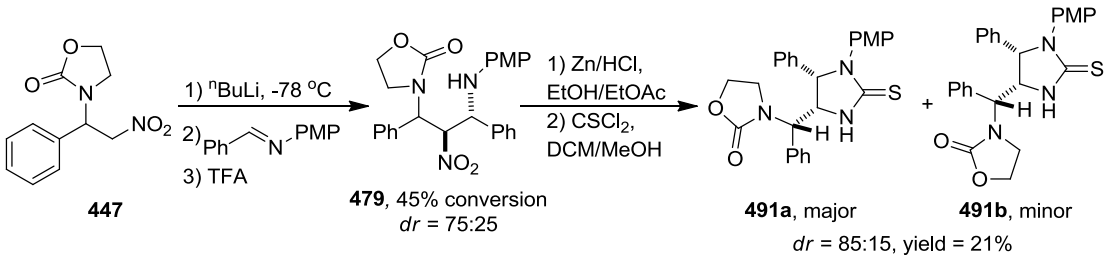


Figure 30. X-ray crystal structures of (±)-**480** and (±)-**482**

To compare with our previous results, it was also attempted to synthesise an imidazolidine-2-thione derivative from oxazolidinone analogue **480**, as was done in section 2.5.6.1. The desired imidazolidine-2-thione was synthesised as a mixture of diastereoisomers **491a** and **491b** with a *dr* of 85:15, in 21% yield over 3 steps (Scheme 167). NOE studies have shown that irradiation of the H_b peak of **491a** at δ 5.78 ppm caused a 2.76% enhancement of the peak of H_c, but only 0.33% of H_a (proton assignments like in Figure 27). The large NOE value between H_b and H_c indicates that the relative stereochemistry between H_b and H_c in the imidazolidine-2-thione ring is *cis*, which agrees with the observed *anti* relative stereochemistry between the nitro group and the amine in *β*-nitroamine **477**. The smaller enhancement between H_b and H_a can be explained by a possible *anti* conformation in the Newman projection between protons H_a and H_b, similar to the one seen previously (Figure 27).

The observed J_{HbHc} value of **491a** was 9.4 Hz, which is again close to the magnitude of that reported for **489** which was 9.2 Hz (Figure 27). This similarity supports the assignment of an *anti* relative stereochemistry between the NO_2 and NH groups in trifluoroacetamide **480**, something that was proved by the X-ray structure obtained. For the minor diastereoisomer **491b**, the J_{HaHb} and J_{HbHc} values observed were 10.0 and 9.8 Hz respectively. The value of J_{HbHc} is almost identical to that of **491a**, so it is fair to assume the same relative stereochemistry around the ring, but the opposite one at the remaining stereocentre. Thereby, it can be concluded that the major diastereoisomer of *β*-nitroamine **479** (*dr* = 75:25) is the *anti/anti* and the minor one the *syn/anti*.



Scheme 167. Synthesis of imidazolidine-2-thiones **491a** and **491b**

Furthermore, some molecular modelling data were collected on trifluoroacetamide **480** and imidazolidine-2-thione **491a** in order to compare with the experimental values and assess the validity of the modelling data. For imidazolidine-2-thione **491a**, both predicted coupling constants were in agreement with the experimental values

(Table 19). For trifluoroacetamide **480**, the predicted value for J_{HaHb} was in agreement with the experimental one, however the experimental value for J_{HbHc} was slightly lower, potentially due to limited contribution by gauche conformations.

Table 19. Experimental and predicted coupling constants of **480** and **491a**

Compound	Coupling constant	*J* observed (Hz)	*J* predicted (Hz)
480	J_{HaHb}	10.1	10.8
480	J_{HbHc}	7.9	10.8
491a	J_{HaHb}	10.7	10.7
491a	J_{HbHc}	9.4	7.8

For *para*-nitroaniline trifluoroacetamide **478**, the observed values of coupling constants were significantly different from the other two analogues. A value of 3.1 Hz was observed for J_{HaHb} and 10.8 Hz for J_{HbHc}. A possible explanation of this would be that trifluoroacetamide **478** still contains a proton capable of hydrogen bonding, so the molecule can form a chair structure like that seen before for other *β*-nitroamines. In this conformation J_{HaHb} would be smaller than expected, while J_{HbHc} would be larger (Figure 31).

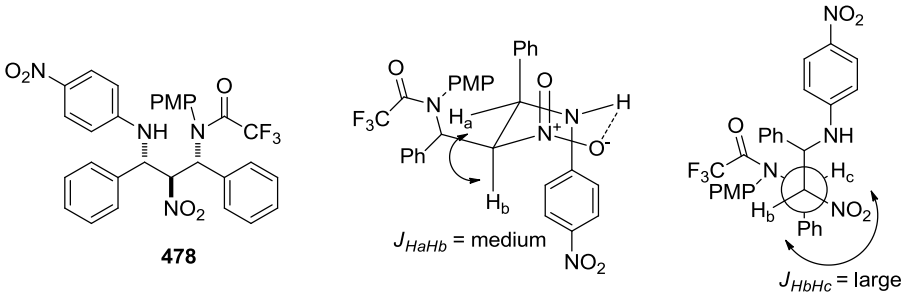


Figure 31

This discrepancy was investigated by molecular modelling studies that predicted the values of J_{HaHb} and J_{HbHc} for the intermediate *β*-nitroamine **477** and trifluoroacetamide **478**.[128] A number of different conformations of *β*-nitroamine **477** were modelled, including ones where *para*-nitroaniline's NH proton was hydrogen-bonded to the nitro group, *para*-anisidine's NH proton was hydrogen-bonded to the nitro group, both the NH protons hydrogen bonded and finally no hydrogen-bonding. The closest agreement to the experimental value was from the model where no hydrogen bonding occurs, with an *anti* conformation over both C-C bonds considered. A number of

different conformations were also modelled for trifluoroacetamide **478**. Those included *para*-nitroaniline's N*H* proton hydrogen-bonding to the nitro group, *para*-nitroaniline's N*H* proton hydrogen-bonding to the TFA group oxygen and no hydrogen-bonding. The closest agreement to the experimental value was interestingly from the model where *para*-nitroaniline's N*H* proton hydrogen-bonded to the TFA group oxygen (Table 20).

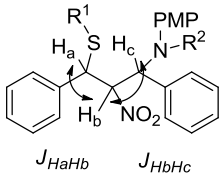
Table 20. Predicted and experimental values of coupling constants of **477** and **478**

Compound	Coupling constant	*J* observed (Hz)	*J* predicted (Hz)
477	J_{HaHb}	9.1	10.7
477	J_{HbHc}	6.2	10.6
478	J_{HaHb}	3.1	1.6
478	J_{HbHc}	10.8	10.8

2.5.6.4 Sulfur adducts

As reported earlier, the nitro-Mannich reaction/TFA-protection methodology gave poor *dr*'s for the two trifluoroacetamides derived from sulfides **485** and **486** (60:40 and 65:35 respectively). In order to assign the relative stereochemistry of both the major and the minor diastereoisomers, we looked at the coupling constants of initially formed *β*-nitroamines **483** and **484** (Table 21). The values of coupling constants though, showed only a small deviation (1.0-2.4 Hz) between the major and the minor diastereoisomers. When looking at the same values for trifluoroacetamides **485** and **486**, it was observed that the values for J_{HbHc} were almost identical in both cases between the two diastereoisomers, while they deviate slightly for J_{HaHb}.

Table 21. Experimental values of coupling constants of the major and minor diastereoisomers of **483-486**.



R^1	R^2 = H		R^2 = TFA	
	J_{HaHb} (Hz)	J_{HbHc} (Hz)	J_{HaHb} (Hz)	J_{HbHc} (Hz)
^{n}Bu, major	11.0	3.5	6.2	10.4
^{n}Bu, minor	8.6	5.9	4.6	10.4
Ph, major	9.4	5.1	5.1	9.8
Ph, minor	10.4	4.0	6.1	10.0

The observed values of J_{HbHc} for both diastereoisomers of *β*-nitroamines **483** and **484** (3.5-5.9 Hz) were in close agreement with those of other carbon, nitrogen and oxygen *β*-nitroamine derivatives (3.4-6.2 Hz, Table 17). Other similar nitroamines prepared in the past were assigned an *anti* relative stereochemistry between H_b-H_c based on J_{HbHc} values of 3.2-5.8 Hz,[114] which agrees with our observed range (Figure 31). In light of this agreement and the fact that an intramolecular hydrogen-bonding chair conformation is assumed, that would fix the J_{HbHc} to medium values for an *anti* relation between the NO_2 and NH groups, leads us to tentatively assign the relative stereochemistry between H_b and H_c as *anti*. Therefore the two diastereoisomers should be the *anti/anti* and the *syn/anti*.

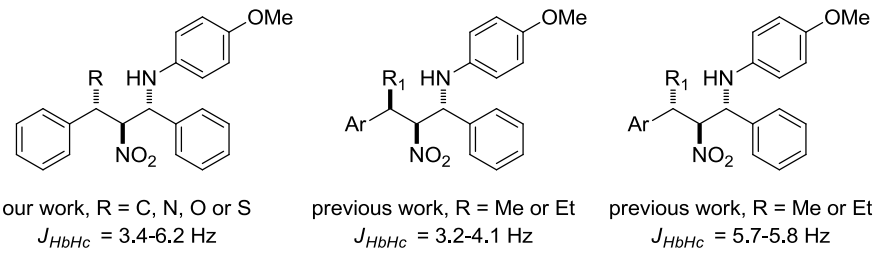


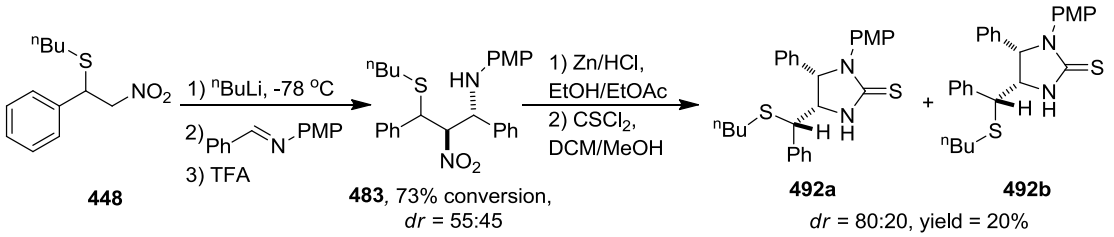
Figure 31. Comparison of J_{HbHc} values of *anti-β*-nitroamines

Molecular modelling data were subsequently collected, in order to help assign the major diastereoisomer. All possible diastereoisomers were modelled and no

significant differences were observed in the values of J_{HaHb} when modelling the lowest energy *anti* conformation of H_a and H_b in the Newman projection (Figure 25). It is unkown how much other rotational conformations contribute to the experimental coupling constant, thus it is very hard to draw any conclusion from this study.

The synthesis of the imidazolidine-2-thione derivatives for the two sulfides was also attempted (Scheme 168), as this has been shown before to be useful for the determination of relative stereochemistry (section 2.5.6.1). Reaction of *β*-nitroamine **483** (*dr* 55:45) was successful in providing imidazolidine-2-thiones **492a** and **492b** with a *dr* of 80:20 (Scheme 168) in 20% yield over 3 steps. Unfortunately, the desired product could not be isolated from the same reaction of phenylsulfide **449**. The J_{HaHb} and J_{HbHc} values of the major diastereoisomer of **492** were 11.5 and 8.4 Hz respectively and for the minor they were 11.2 and 8.8 Hz respectively. Since these values are almost identical, it is very difficult to draw any conclusions of the relative stereochemistry for each diastereoisomer.

NOE studies for the major diastereoisomer of **492** showed that irradiation of the H_b peak at δ 4.58 ppm caused a 4.73% enhancement of the peak of H_c but only 0.41% of H_a. The large NOE value for H_c indicates that the relative stereochemistry between H_b and H_c in the imidazolidine-2-thione ring is *cis*, which agrees with the observed *anti* relative stereochemistry between the nitro group and the amine in *β*-nitroamine **483**. The small NOE value between H_a and H_b, can be explained by a possible *anti* conformation in the Newman projection between protons H_a and H_b, similar to the one seen previously (Figure 27). The *cis* relative stereochemistry between H_b and H_c in the imidazolidine-2-thione ring was also confirmed by the value for J_{HbHc} in the imidazolidinone, which is in agreement to the one reported for **489** (9.2 Hz, Figure 27). The NOE study of the minor diastereoisomer was not possible due to overlapping of the peaks.



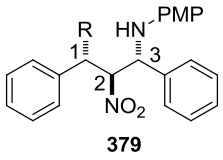
Scheme 168. Synthesis of imidazolidine-2-thiones **492a** and **492b**

It thereby remains uncertain, which is the relative stereochemistry between the SBu and NO_2 groups in *β*-nitroamines **483** and **484** and trifluoroacetamides **485** and **486**. The possible relative stereochemistry of the major diastereoisomer would be suggested in the next section.

In conclusion, our data suggest that in most of our derivatives the nitro-Mannich reaction gives an *anti/anti* relative stereochemistry as the major diastereoisomer formed. All the coupling constant data are given in Appendix 1. In the next section the origins of this diastereoselectivity are discussed.

2.5.7 Source of diastereoselectivity

In the previous sections, it was demonstrated that the two-pot 1,4-addition/nitro-Mannich methodology, starting from *β*-nitrostyrene with non-zinc nucleophiles, showed relative stereocontrol in all three chiral centres formed to give the *anti/anti* diastereoisomers. In previous work with dialkylzinc reagents, the *syn*/*anti* trifluoroacetamides were the major products in homogenous solutions, while the *syn/syn* diastereoisomers were the major products in heterogenous solutions (section 2.1).[35] In light of this, it was important to explain the observed *anti/anti* relative stereochemistry in this work and its difference with the previous results. Products **379** have two pairs of stereocentres that need to be considered, the relative stereochemistry between the nucleophile and the nitro group (C_1-C_2, Figure 32) and the one between the nitro group and the amine (C_2-C_3, Figure 32).

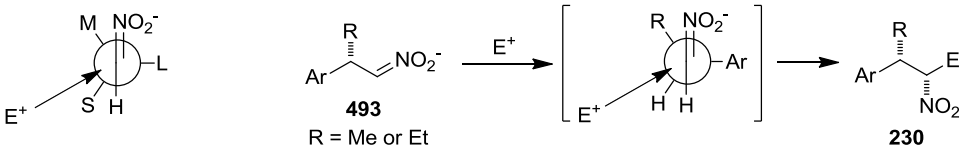


379

Figure 32

The origin of the C_1-C_2 relative stereochemistry is first examined. A number of general rules exist for the electrophilic attack *α*- to a stereocentre, taking under consideration steric and electronic parameters on the stereocentre. According to Houk's outside-crowded model, when considering reactions of highly polarized double bonds, such as enolates and nitronates with electrophiles, the trajectory of the incoming electrophile is the one predicted by the Felkin-Ann model (angle of attack >90° to alkene).[213] According to this model, in the reactive conformation of nitronate

493, the three groups on the adjacent stereocentre are positioned in such a way as the smaller group (S) is closer to the incoming electrophile, the medium one (M) closer to the double bond and the larger one (L) perpendicular to the double bond (Scheme 169). The electrophile would approach from an angle closer to the small group for steric reasons. This analysis correctly predicted the major *syn*-diastereoselectivity observed previously between C_1 and C_2 in the product *β*-nitroamines **230**, in both addition protocols used in the previous work with dialkylzinc reagents (Scheme 169).[35]



Scheme 169. Explanation of the C_1-C_2 *syn* relative stereochemistry reported for dialkylzinc additions to nitrostyrenes.[35]

In light of this it was decided to use Houk's model, described above, to explain the C_1-C_2 stereochemistry in the obtained trifluoroacetamides. This model ignores any stereoelectronic effects that could arise from polar substituents in the adjacent stereocentre. It can be assumed that the substituents in the two carbon adducts **455** and **456** are not polar for the model to be valid. To complete the interpretation, knowledge of the A-values of all groups considered was needed, in order to rank our substituents in the order of size. The reported values for a phenyl group is 2.8 Kcal/mol and for a proton 0.0 Kcal/mol.[214] However, no reported values for the 2,4,6-trimethoxyphenyl and 3-indoline groups exist, as well as for the BuS and PhS groups. In light of this, it was decided to predict the A-values required by calculating the energy difference of the cyclohexane ring bearing the substituent in question in equatorial or axial position, using molecular modelling.[128] The predicted values for MeS, PhS, Me, ^{i}Pr and ^{t}Bu groups were in good agreement with the reported values, while only the phenyl group deviated from the reported A-value (Chart 1). The deviation can be attributed to the fact that the reported values were recorded at rt, whereas the computer calculation assumes a temperature of zero Kelvin with no movement of atoms. Due to this deviation, the predicted A-values for Aromatic substituents were not expected to be accurate.

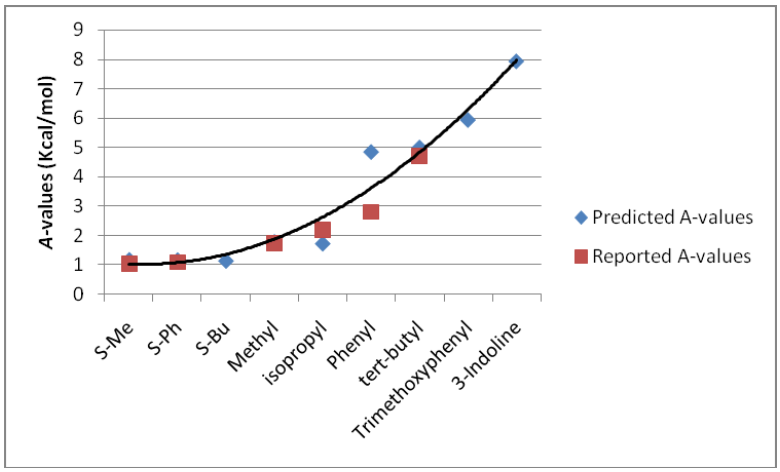
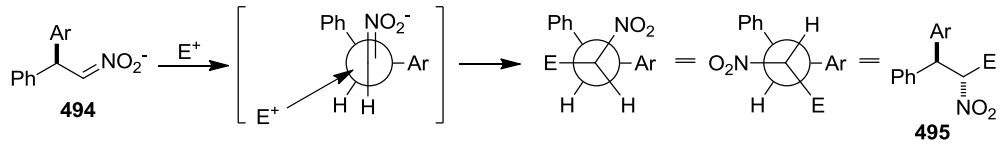


Chart 1. Comparison of calculated and reported[214] A-values of chemical groups

Based on the molecular modelling results, the 2,4,6-trimethoxyphenyl and 3-indoline groups were found to be larger than the phenyl group, with A-values of 5.9 and 7.9 Kcal/mol respectively. These values are too large to be realistic, as A-values much larger than 5 Kcal/mol (^{t}Bu group has 4.7 Kcal/mol) are not expected. However, it can be assumed that the A-values for the 2,4,6-trimethoxyphenyl and 3-indoline groups are indeed larger than the phenyl group.

Applying Houk's model would require that the Ar group (2,4,6-trimethoxyphenyl or 3-indoline group) would occupy the *anti* position to the incoming electrophile in the reactive conformation of nitronate **494**, with the phenyl group being inside and the proton being in the crowded outside position (Scheme 170). The reaction will then proceed *via* the Newman projection shown in Scheme 170, which has an *anti* stereochemistry between the Ar and NO_2 groups in *β*-nitroamines **495**.



Scheme 170. Origin of the C_1-C_2 relative stereochemistry when Ar is bigger than Ph

A different explanation however, is needed for the rest of our examples, as a variety of different heteroatoms are present in the adjacent stereocentre. Consequently, stereoelectronic effects that arise from the presence of polar substituents in the adjacent stereocentre of nitronate **496** are now important. Even though the Felkin-Ahn model predicts that the electronegative substituent would occupy the perpendicular

position in nucleophilic additions to double bonds,[215] it is less clear what the reactive conformation is in electrophilic additions.[216]

Some reports in the literature however, were helpful in understanding the stereoelectronic effects in the reaction of our nitronates. Very useful to the understanding of the model of electrophilic addition reactions to electron rich double bonds, was the report by Houk and co-workers on the stereoselective cycloadditions of nitrile oxides to chiral allyl ethers and alcohols.[213] The authors reported a preference of alkoxy and hydroxyl groups to occupy the inside position, while other alkyl or aryl groups occupy the *anti* position and the proton the remaining outside position (transition state A, Figure 33). The authors argue that the reason for the preference of the alkoxy group for the inside position is that during the attack of the electrophile, the π bond becomes electron deficient so electron-withdrawing groups would destabilize the transition state. If the alkoxy group is in the *anti* position then the σ^*_{CO} overlaps with the π orbital of the alkene, withdrawing electron density from it. When C-O is inside however, this overlap is minimised, while overlap of electron donating σ_{CH} and σ_{CR} with the π bond is maximised thereby stabilizing the transition state. The authors also suggest that the second most favourable transition state would be B, where the alkoxy group is positioned outside and the proton inside. Transition state B is less favoured, as it places the OR group *gauche* to the alkene's H, something that would increase the steric clash to the incoming electrophile.

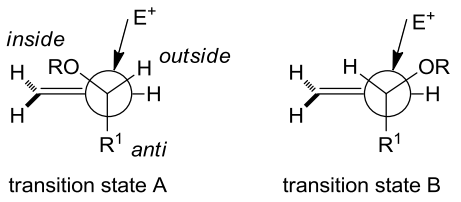
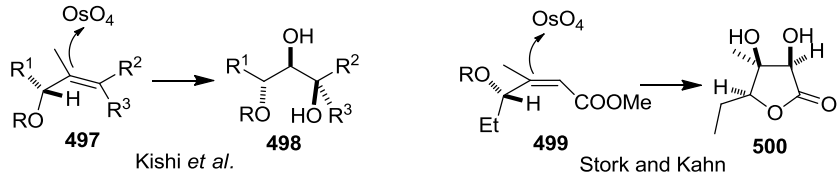


Figure 33. Houk's model of electrophilic additions to electron rich double bonds

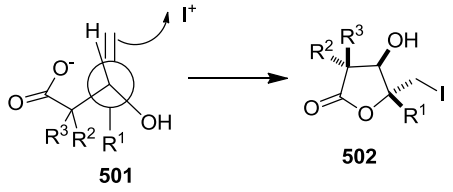
Houk and co-workers argue that their inside alkoxy model can be used to explain other electrophilic additions to allyl ethers. When studying the osmylation of allylic ethers **497**, Kishi and co-workers reported a good level of diastereoselectivity, that could not be explained by considering the steric factors only. The major diastereoisomers of the product diols **498**, were the ones where the newly formed hydroxyl group was *trans* to a pre-existing hydroxyl or ether group, suggesting an *anti* attack of the reagent to the oxygen atom (Scheme 171).[217,218] In a similar work Stork

and Kahn reported the hydroxylation of α,β-unsaturated esters **499** by OsO_4, to give diastereomerically pure 3,4-dihydroxy-γ-lactones **500**.[219] In this work, the authors suggest a different mechanism where the alkoxy group is in the outside position, which is the same as transition state B proposed by Houk (Figure 33). They argue that a favourable interaction exists between the π bond and the γ-oxygen's lone pair because of the electron withdrawing character of the carbomethoxy functionality.



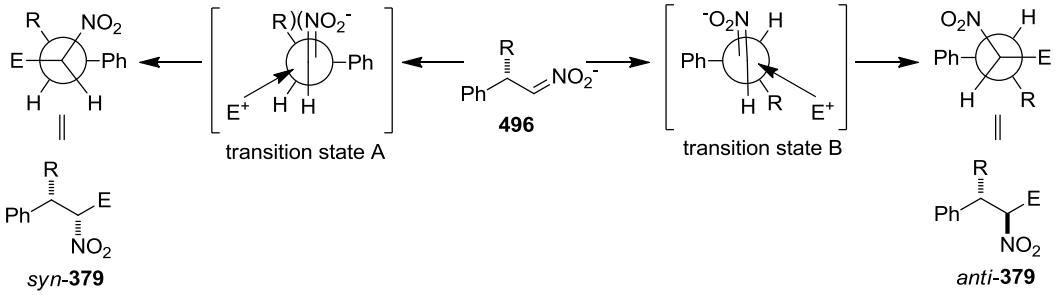
Scheme 171. Kishi's and Stork's electrophilic additions to electron rich double bonds

Furthermore, when studying the iodocyclisation of allylic alcohols **501**, Chamberlin and co-workers reported a transition state for the electrophilic addition of iodine similar to Houk's B model (Figure 33), which explains their high diastereoselectivity of lactones **502** produced (Scheme 172).[220]



Scheme 172. Chamberlin's electrophilic addition of iodine to double bonds

Based on the reported results, it can be assumed that one of the two models proposed by Houk (Figure 33) would be valid in our case, when we have an electronegative substituent (R) in the stereocentre adjacent to the nitronate **496**. After a closer look into the two transition states (Scheme 173), it becomes apparent that transition state A would be destabilised by the repulsion of the nitro group with group R, as both of these groups are electron rich. Therefore, it would not be preferred for them to be close in space (Scheme 173). Such repulsion was not present in the above examples, as they lack an electron rich group on the double bond. Therefore, we can expect transition state B to be in operation when R is an electronegative substituent, with the Ph group, being larger than H, occupying the perpendicular position and the proton the inside position, giving rise to *anti*-**379** β-nitroamines (Scheme 173).



Scheme 173. Origin of the C_1-C_2 relative stereochemistry when R is an electronegative substituent

The above reasoning correctly predicts the observed *anti* relative stereochemistry between the groups R and NO_2 in most of our derivatives. However, for the two sulfides **485** and **486** a very poor *dr* was observed (60:40 and 65:35 respectively), which shows that two competitive transition states are in operation that have a small energy difference. If sulfur is treated as an electronegative substituent, then transition state B would prevail where sulfur occupies the perpendicular position (Scheme 173). However, the reported value of electronegativity of sulfides is only 1.69, while that of the phenyl group is 3.64, which contradicts this hypothesis.[221] Moreover, the reported A-value for PhS is 1.1 Kcal/mol, while the predicted value for ^{n}BuS is again 1.1 Kcal/mol (Chart 1). Both these values are smaller than the A-value of the Ph group (2.8 Kcal/mol).[214] Therefore, it is expected that the phenyl group would occupy the perpendicular position in the reactive conformation of **496** and both the transitions states A and B would be in operation (Scheme 173). A preference to transition state A would be expected, as the C-S bond is longer than the C-O or C-N ones and sulfur has less electron density (softer), thus it is expected to have less repulsion to the nitro group. Furthermore, transition state A is the one predicted by the Felkin-Ahn model, as it has the smallest group (H) closer to the incoming electrophile. Consequently, the major diastereoisomers of **503** in the two sulfide reactions can tentatively be assigned as the ones having a *syn/anti* relative stereochemistry (Figure 34).

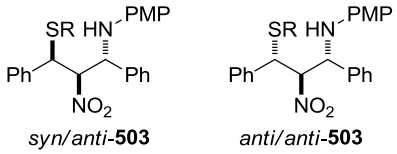
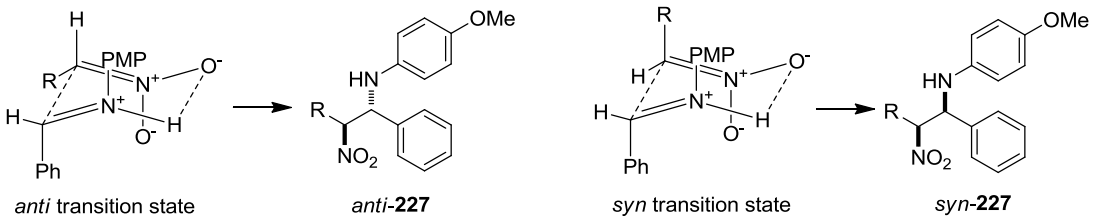


Figure 34

Having examined the origin of the C_1-C_2 relative stereochemistry, a plausible transition state model will now be formulated, in order to explain the origin of relative

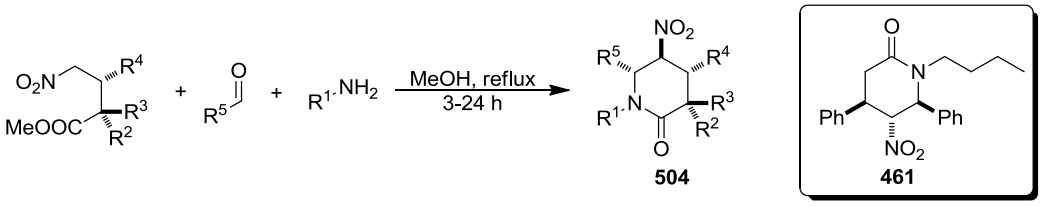
stereochemistry across the C_2-C_3 stereocentres. The observed stereochemistry was in all of our examples *anti*, which implies a common mechanism. As was previously suggested for the conjugate addition/nitro-Mannich reactions of Superhydride® to nitroalkenes,[36] it is postulated that the nitro-Mannich reaction proceeds *via* a Zimmerman-Traxler type transition state (Section 2.5.6). The most favoured transition state was the one leading to the *anti* isomer, as it avoids the 1,3-diaxial interactions between the axial R group and the PMP group, present in the transition state leading to the *anti* isomer (Scheme 174).



anti transition state | *anti*-**227** | *syn* transition state | *syn*-**227**

Scheme 174. Origin of the C_2-C_3 relative stereochemistry

Finally, the origin of the *trans/trans* relative stereochemistry in piperidinone **462** was investigated. The reaction was inspired from the work of Dixon and co-workers, who reported the synthesis of densely substituted pyrrolidinones by refluxing nitroesters with imines and benzoic acid (Scheme 76, section 1.5).[11] The synthesis of piperidinones of this kind, starting from nitroesters, aldehydes and amines, has also been reported by the same group (Scheme 175).[222] Piperidinones **504** were isolated mostly as single diastereoisomers bearing a *trans/trans* relative stereochemistry. The authors suggested two possible explanations to this, both supported by their experimental results. The first hypothesis was that the nitro-Mannich reaction was reversible and only one of the produced diastereoisomers cyclises preferentially in the irreversible lactamisation step, to give the most thermodynamically stable product. The second hypothesis was that two of the nitro-Mannich products cyclise and epimerization then occurs on the centre bearing the nitro group, leading to the most thermodynamically stable product. Likewise, in our experiment we can postulate either of these two hypotheses to be valid. No attempt to mechanistically investigate this reaction was made and no possible intermediates isolated, as this reaction was only performed to compare to our deprotonation/nitro-Mannich methodology.



Scheme 175. Relative stereochemistry of piperazinone **462**

2.5.8 Conclusions

This chapter described the investigation of the conjugate addition/nitro-Mannich reaction of non-zinc nucleophiles to nitroacrylate **231** and *β*-nitrostyrene **380**. A variety of different nucleophiles were tested, including amines, thiols, phosphines, alcohols, enolates and nitriles. It was found that a two-pot procedure was more successful than a one-pot procedure. From nitroacrylate **231**, the 1,4-addition products were isolated generally in good yields (81-99%) and then deprotonated with ^{n}BuLi and reacted with imine **281** and TFA. However, the success of this methodology was limited, as in most examples the pyrrolidinone products could not be isolated, while some of the isolated ones were found to be unstable. A few stable products were isolated, such as the highly functionalised pyrrolidinones **420** and **421** and octahydroquinoline **422** (Figure 35).

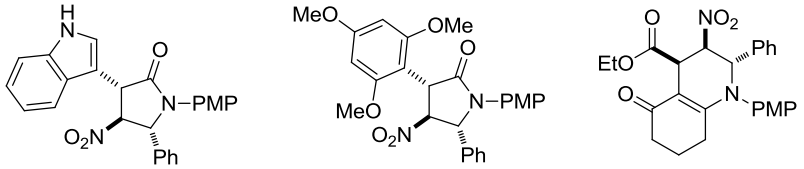
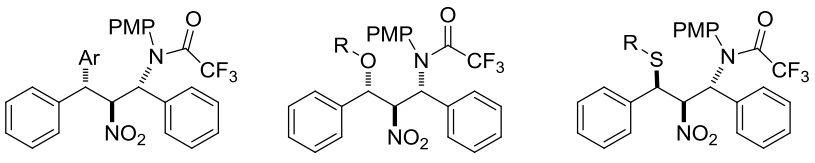


Figure 35

The conjugate addition of the same range of nucleophiles to *β*-nitrostyrene gave variable yields of 1,4-addition products **428** (45-97%). After deprotonation and nitro-Mannich reaction, the isolated *β*-nitroamines **379** were protected as trifluoroacetamides, as they were unstable to purification. The reaction of adducts of aromatic groups was successful and trifluoroacetamides **505** were isolated in medium yields as single diastereoisomers, whereas reactions of nucleophilic methylene adducts were mostly ineffective. Nitro-Mannich reactions of alcohol adducts gave good yields of trifluoroacetamides **506** and excellent diastereoselectivities. Reactions

of adducts of amines were mostly ineffective and only small yields of products were isolated in limited cases. Thiol adducts gave the desired trifluoroacetamides **507**, albeit in medium yields and poor diastereoselectivities, while adducts of phosphines reacted poorly (Figure 36).

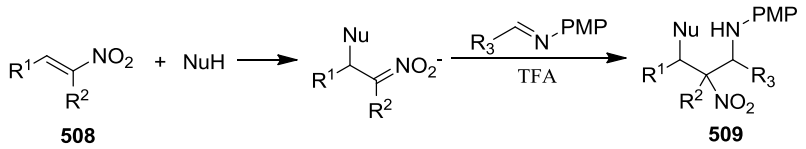


505, 50-83%, *dr* > 95:5 **506**, 64-80%, *dr* > 95:5 **507**, 47-56%, *dr* = 60:40

Figure 36

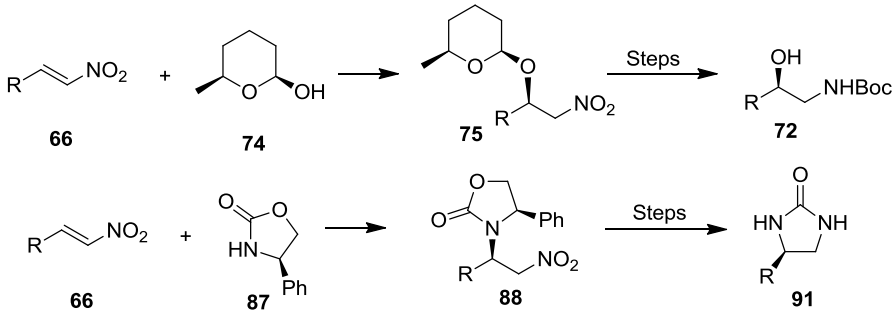
2.5.9 Future work

This chapter described the investigation of the 1,4-addition/nitro-Mannich reaction using non-zinc reagents. A comprehensive investigation was made into the conjugate addition of various reagents into nitroalkenes **231** and **380** and the feasibility of a nitro-Mannich reaction of the resulting nitroalkanes, however there is still plenty of work that could be carried out. Firstly, while this work was focused on the reactions of nitroalkenes **231** and **380**, a wide variety of nitroalkenes exist, accessed easily from condensation of commercial aldehydes with nitromethane, followed by dehydration.[190] Therefore, this study could be expanded to other nitroalkenes, especially trisubstituted ones **508** (Scheme 176). Such nitroalkenes were shown to react successfully in conjugate addition reactions (sections 1.2.3 and 1.2.4) and might offer a solution to some degradation issues encountered in this study, as they might be less prone to degradation by polymerisation due to steric reasons. Furthermore, this work focused on imine **281** and no other aromatic, heteroaromatic or alkyl imines were investigated. The investigation presented in this thesis offered the knowledge on which nucleophiles are more efficient in the reaction with β-nitrostyrene. The most effective nucleophiles were found to be electron-rich aromatics and alkoxides. Therefore, the investigation of the reactions of aromatic and alkoxy nucleophiles could be expanded to a combination of a variety of other nitroalkenes and imines, to give a wide range of possible products **509** (Scheme 176).



Scheme 176. Possible conjugate addition/nitro-Mannich reactions

Furthermore, a variety of methods exist for performing asymmetric 1,4-additions to nitroalkenes using chiral catalysts (sections 1.2.3, 1.2.4 and 1.2.5). It would therefore be expected that if the conjugate addition to the nitroalkene was asymmetric, this would control the stereochemistry of all three newly formed stereocentres, giving rise to enantioenriched products. Alternatively, a chiral nucleophile could be used in the 1,4-addition reaction, something that should control the stereochemistry of the nitro-Mannich reaction. The chiral functionality could then potentially be removed to uncover highly functionalised enantioenriched products. Two promising examples of such reagents were reported, the "chiral water" reagent **74** developed by Dixon and co-workers and chiral oxazolidinone **87** developed by Le Gall and co-workers (Scheme 177).[54,58]



Scheme 177. Asymmetric additions of **75** and **87** to nitroalkenes

2.6 The synthesis of *piperazirum via* the nitro-Mannich methodology

2.6.1 Isolation

A number of biologically active piperazines exist. Many possess useful pharmaceutical properties, such as the HIV protease inhibitor indinavir **510** developed by Merck, as well as other experimental drugs.[223] When studying the flowering plant *Arum Palaestinum*, Kim and co-workers isolated a new alkaloid compound from the ^{n}butanol fraction of the plants' leaves which they named *piperazirum*.[224] After structure elucidation through spectroscopic techniques (Mass spec., IR, ^{1}H and ^{13}C NMR), *piperazirum* was shown to be piperazinone **511** (Figure 37). Some studies of

the biological activity of this molecule showed that it exhibited inhibitory activity to a number of human cancer cell lines.[224] Due to the activity of *piperazirum* as an anticancer agent and the presence of a 1,2-diamine functionality in the proposed structure **511**, together with the absence of a synthetic route to such a simple looking small molecule, it was felt that the nitro-Mannich methodology previously developed in the Anderson group could be used in the synthesis of this molecule.

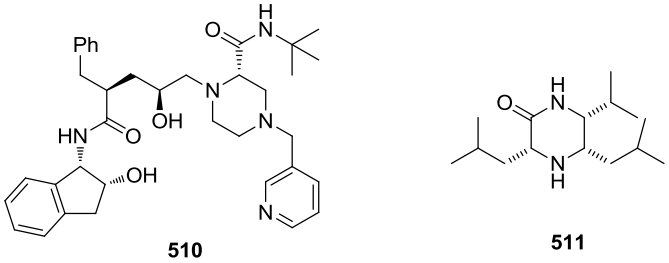
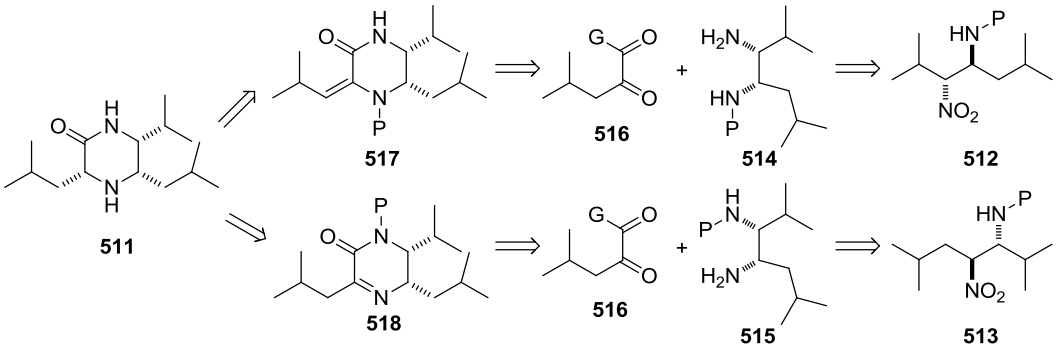


Figure 37. Biologically active piperazines

2.6.2 Strategy

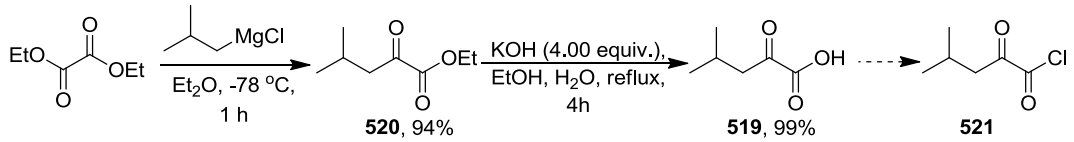
A retrosynthetic analysis of **511**, showed that the 1,2-diamine motif present could come from *β*-nitroamine **512** or **513**, derived from a suitable nitro-Mannich reaction (Scheme 178). A simple condensation of diamine **514** or **515** with a suitable ketoacid derivative **516**, should give enone **517** or **518**. Further diastereoselective reduction and deprotection steps should provide **511**. If the synthesis of *β*-nitroamine **512** or **513** was rendered asymmetric, then the enantiomerically pure form of **511** could be accessed. The natural compound was isolated as a single enantiomer, though the absolute stereochemistry has not been assigned by X-ray crystallography. Initially a racemic route was attempted with the hope that an asymmetric variant of the nitro-Mannich reaction could later be developed.



Scheme 178. Retrosynthetic analysis of piperazine **511**

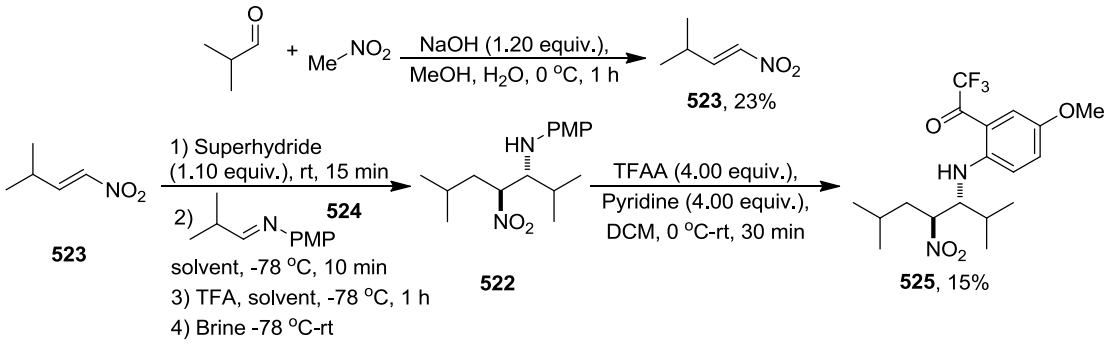
2.6.3 Synthesis

Initially, the synthesis of useful ketoacid **519** was investigated. Ketoester **520** was easily synthesised from a Grignard reaction of isobutyl magnesium chloride with diethyloxalate in 94% yield (Scheme 179).[225] Saponification of ketoester **520** with KOH then provided ketoacid **519** in excellent yield,[226] while the respective acid chloride **521** could easily be prepared *in situ* by treatment with oxalyl chloride (Scheme 179).[227]



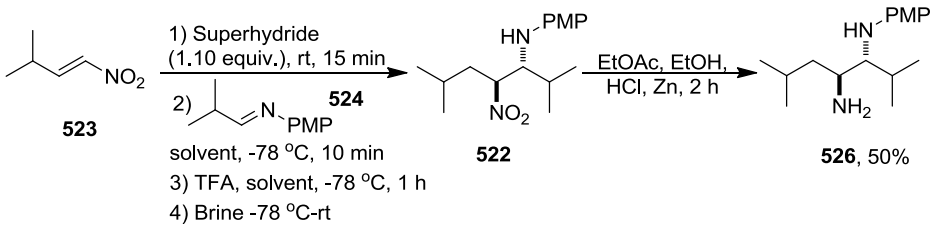
Scheme 179. Synthesis of ketoester **520** and ketoacid **519**

With the ketoacid derivatives in hand, the synthesis of a suitable *β*-nitroamine was investigated. The synthesis of *β*-nitroamine **522** was attempted using nitroalkene **523** and imine **524** (Scheme 180). The 1,4-addition of Superhydride® on nitroalkenes and subsequent nitro-Mannich reaction has been reported by the Anderson group, to give *anti* rich *β*-nitroamines **227** (scheme 77, section 2.1).[36] Nitroalkene **523** was synthesised in one step from isobutyraldehyde and nitromethane (Scheme 180).[228] Imine **524** was synthesised by the simple condensation of the same aldehyde and *para*-anisidine with basic alumina, in DCM, at -78 °C, in 86% yield and used immediately to avoid degradation. The 1,4-addition of Superhydride® and subsequent nitro-Mannich reaction with imine **524** in THF gave *β*-nitroamine **522** in 64% conversion and 70:30 *dr*. Using previously developed conditions to protect the amine *in situ* using TFA-anhydride gave no trifluoroacetamide, but only nitroamine **525** was isolated as a single diastereoisomer in a low 15% yield. This result is not surprising as poor conversions and *dr*, as well as resistance to TFA-protection were observed before with imines disubstituted in the *α* position, such as cyclohexyl imine.[36]



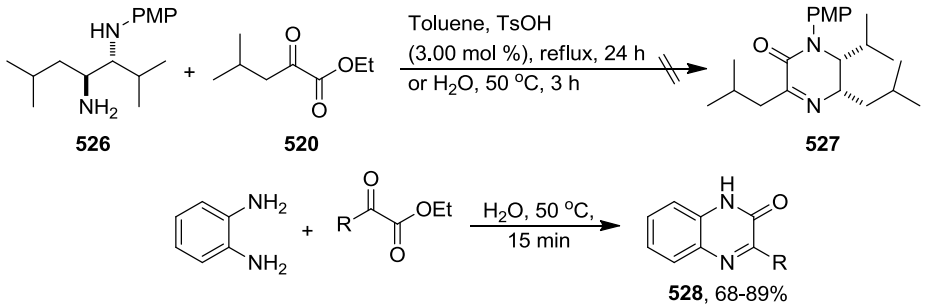
Scheme 180. Nitro-Mannich reaction from nitroalkene **523**

The low yield of product **525** from the above reaction, as well as the fact that an electrophilic aromatic substitution reaction occurred instead of TFA-protection, meant that this product could not be used in our synthesis. However, as the conversion to intermediate *β*-nitroamine **522** was good, it was decided to avoid the TFA-protection step and reduce the nitroamine directly to 1,2-diamine **526**. The isolation and reduction of *β*-nitroamines such as **522**, suffers from the instability of these products due to retroaddition. However, it was found previously that it was possible to isolate *β*-nitroamines **230b** by performing a column chromatography with no delay and gaining all possible data as fast as possible in cases where the products could not be TFA-protected (Scheme 78, section 2.1).[35] Moreover, in previous studies samarium diiodide[13] or aluminium amalgam[37] were used to reduce *β*-nitroamines. Instead of these methods, a simpler method was attempted, the treatment of the *β*-nitroamine with Zn/HCl. After the nitro-Mannich reaction, the crude *β*-nitroamine product **522** was isolated by column chromatography and then immediately treated with Zn dust (10.0 equiv.) and 6 M aqueous HCl (20.0 equiv.) in EtOAc and EtOH, at rt for 2 h. The resulting diamine **526** was isolated in 50% overall yield as a single diastereoisomer (Scheme 181).



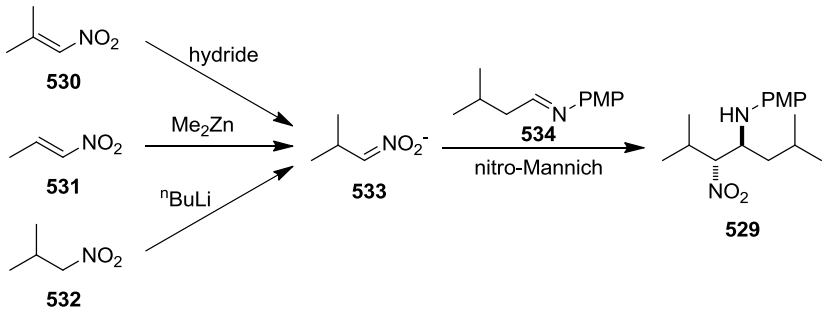
Scheme 181. Synthesis of diamine **526**

With diamine **526** in hand, the reaction with a suitable ketoacid derivative was investigated. The most reactive nitrogen was expected to be the primary amine. The most electrophilic carbonyl in ester **520** should be the ketone, as shown by reports on the reactivity of similar compounds.[229,230] Therefore, the condensation of these two molecules should give 5,6-dihydropyrazin-2-one **527**. The reaction under Dean-Stark conditions, after refluxing in toluene for 24 h in the presence of catalytic TsOH, gave only recovered starting materials. Simple heating of a 1,2-diamine with a ketoester in water at 50 °C was reported to give quinoxalinones **528** (Scheme 182).[231] However, under these conditions, only a complicated mixture of products was isolated.



Scheme 182. Attempt to synthesise 5,6-dihydropyrazin-2-one **527**

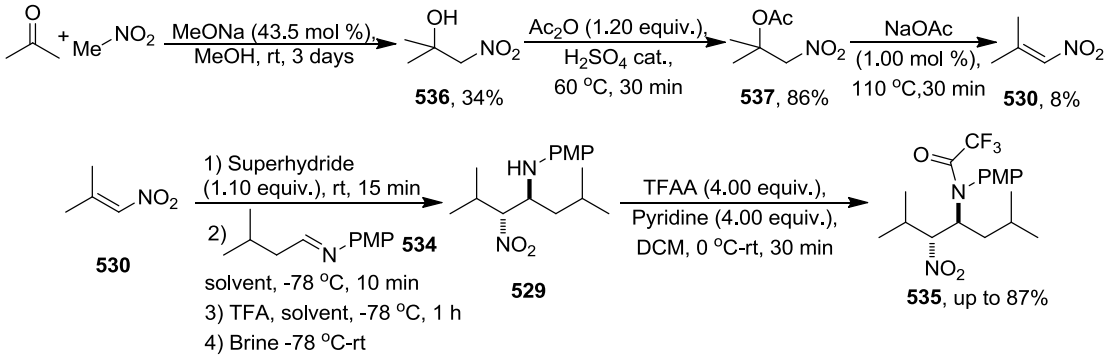
In light of this poor result, an alternative route to **511** *via* *β*-nitroamine **529** was investigated. For the synthesis of *β*-nitroamine **529**, three possible methods were considered, starting from nitroalkenes **530** and **531** as well as from nitroalkane **532** (Scheme 183). Nitro-Mannich reaction of nitronate **533** with imine **534** should provide *β*-nitroamine **529**. Nitronate **533** can be formed in three possible ways, from an addition of hydride to nitroalkene **530**, addition of Me_2Zn to nitroalkene **531** or deprotonation of nitroalkane **533** (Scheme 183).



Scheme 183. Possible routes to nitroamine **529**

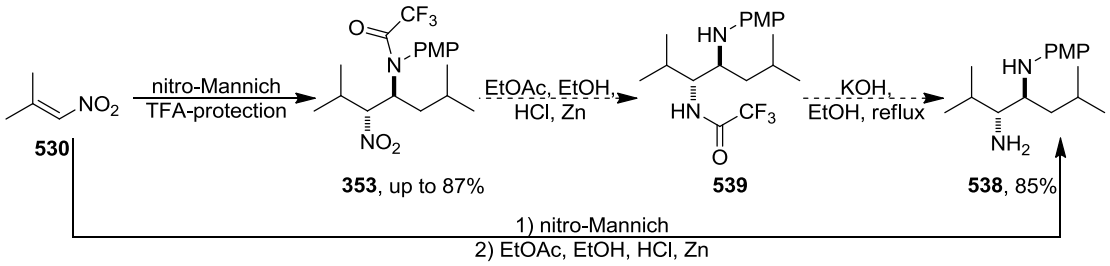
The 1,4-addition/nitro-Mannich reaction of nitroalkene **530** with Superhydride® and imine **534** was initially investigated. Nitroalkene **530** was synthesised in three steps

from acetone and nitromethane, in low overall yield (Scheme 184).[232] Imine **534** was synthesised by the simple condensation of isovaleraldehyde and *para*-anisidine with basic alumina, in DCM, at -78 °C, in 95% yield and used immediately to avoid degradation. The reductive nitro-Mannich reaction with imine **534** in THF gave *β*-nitroamine **529** in complete conversion and 85:15 *dr* and after TFA-protection trifluoroacetamide **535** in 78% yield and 95:5 *dr*. In previous work, improved *anti*-selectivity was observed when DCM was used as the solvent, therefore the reaction was repeated using DCM.[36] Indeed, with DCM complete conversion to *β*-nitroamine **529** was observed with a *dr* of >95:5 and after TFA-protection, trifluoroacetamide **535** was isolated in 87% yield as a single diastereoisomer.



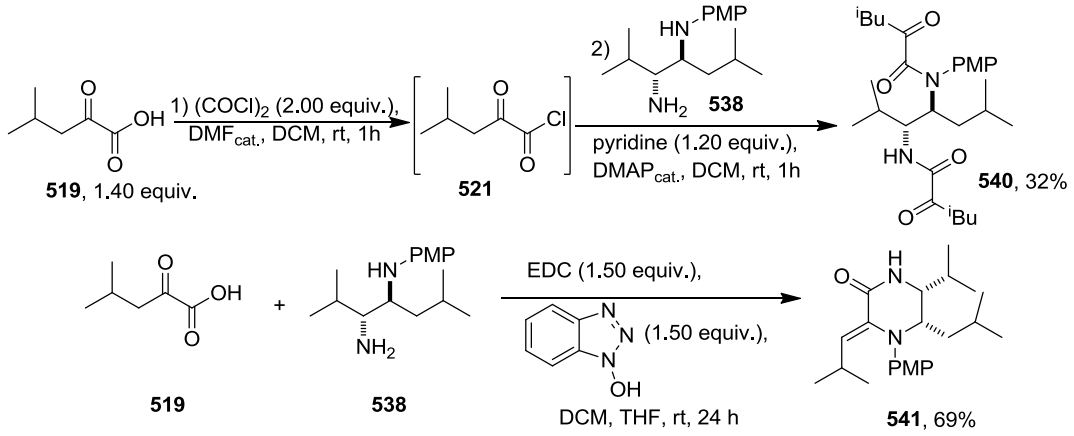
Scheme 184. Synthesis of nitroalkene **530** and trifluoroacetamide **535**

After successfully obtaining trifluoroacetamide **535** in good yield, the synthesis of the corresponding diamine **538** was attempted. Transforming trifluoroacetamide **535** to 1,2-diamine **538** would require two further steps, specifically reduction with Zn/HCl to trifluoroacetamide **539** and then treatment with KOH to deprotect the trifluoroacetamide and release the amine **538**, as has been previously reported (Scheme 185).[233] Therefore, the direct reduction of *β*-nitroamine **529** to 1,2-diamine **538** was investigated, avoiding the two extra steps. After the nitro-Mannich reaction, the crude *β*-nitroamine **529** product was isolated by column chromatography and then immediately treated with Zn dust (10.0 equiv.) and 6 M aqueous HCl (20.0 equiv.) in EtOAc and EtOH, at rt for 2 h. The resulting diamine **538**, was isolated in 85% overall yield as one diastereoisomer (Scheme 185).



Scheme 185. Synthesis of diamine **538** from nitroalkene **530**

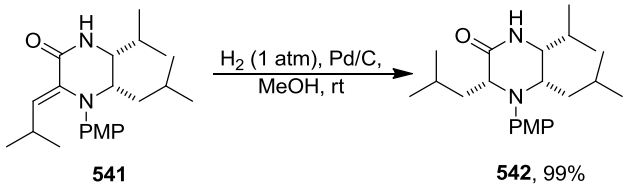
In diamine **538** it would again be expected that the most reactive amine group would be that of the primary amine. To obtain a piperazinone of the desired geometry, a ketoacid derivative would be required, where the carboxylate carbonyl is more reactive than the ketone one. Two possible such compounds were considered, carboxylic acid **519** after activation by a coupling agent and acid chloride **521**. Acid chloride **521** was prepared *in situ* by treatment of acid **519** with oxalyl chloride (2.00 equiv.) and catalytic DMF. Subsequent reaction with diamine **538** in the presence of pyridine (1.20 equiv.) and catalytic DMAP, over 24 h, according to previously reported reactions for similar ketoacids,[227] gave only the bis-adduct **540** and none of the desired piperazinone **541**. The reaction of carboxylic acid **519** though, with diamine **538**, in the presence of EDC (1.50 equiv.) and 1-hydroxybenzotriazole (1.50 equiv.) at rt, gave the desired product **541** in good yield (Scheme 186).[234] The assignment of the relative stereochemistry of **541** will be described in section 2.6.4.



Scheme 186. Synthesis of piperazinone **541**

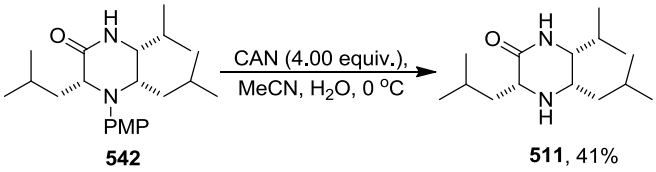
Having successfully synthesised piperazinone **541**, the reduction of the double bond was then required. Reduction of such enones has been reported using H_2 over Pd/C. The relative stereochemistry of **541** should render the hydrogenation

diastereoselective as the catalyst would be expected to approach the molecule from the less sterically hindered top face. Indeed, the hydrogenation in MeOH, at rt with only 1 atm of H_2 (balloon) afforded piperazinone **542** as a single diastereoisomer (Scheme 187). The assignment of relative stereochemistry of **542** will be described in section 2.6.4.



Scheme 187. Hydrogenation of piperazinone **541**

The final step required to complete the synthesis of **511**, was the deprotection of the PMP group in piperazinone **542**. This deprotection can be affected using oxidation by CAN in $MeCN/H_2O$, at 0 ^oC.[116] These conditions successfully affected the deprotection of **542** to give the desired piperazinone **511** in 41% yield (Scheme 188). Our compound **511** has the correct relative stereochemistry as proposed for the natural product (section 2.6.4). However, the ^1H NMR and ^{13}C NMR data did not match the data given for the natural product. The details on structure elucidation of **511** will be described in the next section.

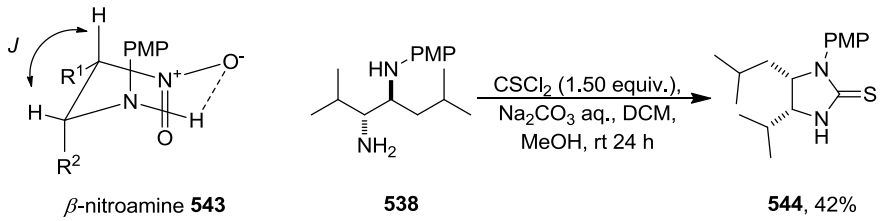


Scheme 188. Deprotection of piperazinone **542**

2.6.4 Relative stereochemistry

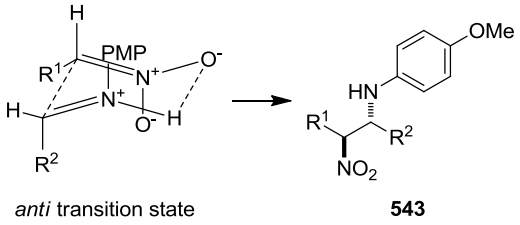
The conjugate addition/nitro-Mannich reaction of Superhydride® to nitroalkenes was reported to give *anti*-rich *β*-nitroamines **227** (Scheme 77, section 2.1).[36] Even thought this was the predicted relative stereochemistry for the *β*-nitroamines synthesised in this work, confirmation was needed. The *β*-nitroamines from this work (**543**) are expected, like before, to reside in a *pseudo*-chair conformation in solution (Scheme 189).[115] The coupling constants expected between protons C*H*NO_2 and C*H*NH for *anti*-**543** would therefore be expected to be of medium value. The values for *β*-

nitroamines **522** and **529** were 3.8 and 8.1 Hz respectively and are in agreement with the reported values for *anti*-*β*-nitroamines, which were in the range of 4.5-8.4 Hz.[233] Moreover, the synthesis of imidazolidine-2-thione **544** from diamine **538** was attempted in order to further confirm the *anti* relative stereochemistry of the initial *β*-nitroamine **529**. In the same way as before (section 2.5.6.1), reaction with thiophosgene gave imidazolidine-2-thione **544** in 42% yield as a single diastereoisomer (Scheme 189). NOE studies showed that irradiation of the C*H*NH peak at *δ* 3.70 ppm caused a 3.65% enhancement of the C*H*N peak, indicating a *cis*-relative stereochemistry between the two protons, which agrees with the observed *anti* relative stereochemistry between the nitro group and the amine in *β*-nitroamine **529** (Scheme 189). The observed coupling constant between the same two protons was 8.4 Hz, a value that is in agreement with the one reported for **489** which was 9.2 Hz (Figure 27, section 2.5.6.1), further corroborating our assignment.



Scheme 189. Synthesis of imidazolidine-2-thione **544**

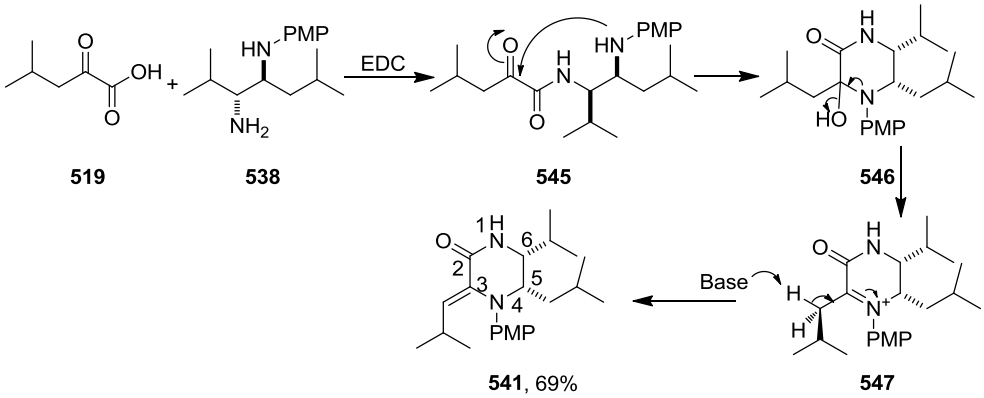
The origin of the observed *anti* stereochemistry tentatively lies in the mechanism of the nitro-Mannich reaction, that is thought to proceed *via* a Zimmerman-Traxler type transition state (Section 2.5), as was previously suggested (Scheme 190).[36]



Scheme 190. Relative stereochemistry of *β*-nitroamine **529**

The relative stereochemistry of 5,6-dihydropyrazin-2-one **541** was consequently examined. The relative stereochemistry of the C^5-C^6 stereocentres of **541** follows from the *anti* relative stereochemistry of acyclic diamine **538** which originated from the nitro-Mannich reaction. The double bond geometry was assigned by NOESY ^{1}H NMR to have *Z* stereochemistry (Scheme 191). The reason for this stereochemistry

could be explained by the following mechanism (Scheme 191). Initial reaction of ketoacid **519** and diamine **538** should give ketoamide **545**. Intramolecular nucleophilic addition of the secondary amine to the free carbonyl group would give **546**, which after loss of water assisted by the nitrogen lone pair forms compound **547**. The final deprotonation would occur in an antiperiplanar alignment to the C=N bond. There are two protons that can be eliminated, one giving the *Z* and the other the *E* isomer. Presumably the isopropyl group attached on the site of elimination in **547** would prefer to be on the top face as drawn, avoiding a destabilising interaction with the ^{i}Pr and ^{i}Bu groups on the underface. Elimination would give the observed *Z* isomer of enone **541**.



Scheme 191. Origin of the relative stereochemistry of piperazinone **541**

The hydrogenation of enone **541** was expected to preferentially afford piperazine **542**. The expected *cis*/*cis* relative stereochemistry was indeed observed. NOE studies have shown that irradiation of the H^3 peak at δ 4.09 ppm caused a 0.17% enhancement of the H^6 peak and negligible enhancement of the H^5 peak. Irradiation of the H^5 peak at δ 3.37 ppm caused a 2.90% enhancement of the H^6 peak and a 0.07% enhancement of the H^3 peak. The NOE data suggests that protons H^5 and H^6 are close in space, confirming a *cis* relative stereochemistry. Moreover, the observed coupling constant between the same two protons was 3.3 Hz, a value that is typical between adjacent axial and equatorial protons in cyclohexane rings.[235] The very small NOE between protons H^3 and H^5 indicates that these two protons could be in equatorial positions, therefore further apart than are protons H^3 and H^6, which would have an axial-equatorial relationship explaining the higher NOE in this case. Molecular modelling of piperazine **542** showed that indeed the conformation having the isopropyl group equatorial and the two isobutyl ones in axial positions was lower in energy than the

ring flipped conformation (Figure 38). The predicted values for the distances between the three protons H^3, H^5 and H^6 for the axial/axial/equatorial conformer of **542** were indeed in agreement with the magnitudes of our NOE data (Figure 38).

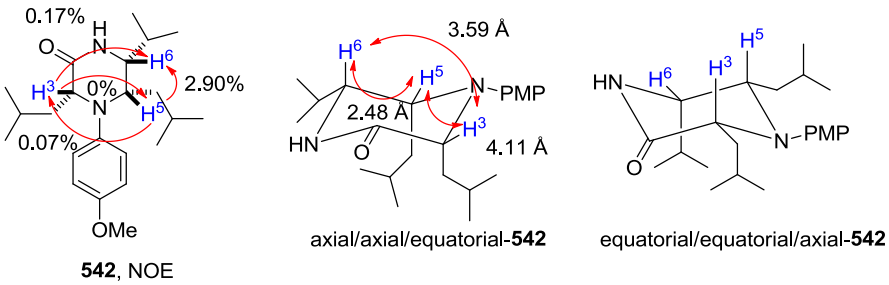


Figure 38

It was expected that the desired piperazinone **511** formed by deprotection of **542** would have the same *cis*/*cis* relative stereochemistry as the starting material, which is also the one assigned by the authors for the natural compound piperazirum.[224] NOE studies have shown that irradiation of the H^3 peak at δ 3.40 ppm caused a 1.10% enhancement of the H^5 peak and 0.10% enhancement of the H^6 peak. There seems to be a change from the NOE data for PMP-protected **542** where proton H^3 was shown to be closer to H^6 than to H^5. This change could be attributed to a different conformation of piperazinone **511**, as confirmed by molecular modelling (Figure 39). If equatorial/equatorial/axial-**511** is now the prevalent conformation, then protons H^3 and H^6 have an axial-equatorial relationship, while H^3 and H^5 have an axial-axial one explaining the higher NOE in this case. The coupling constant of protons H^3 and H^5 could not be distinguished from the ^{1}H NMR spectrum.

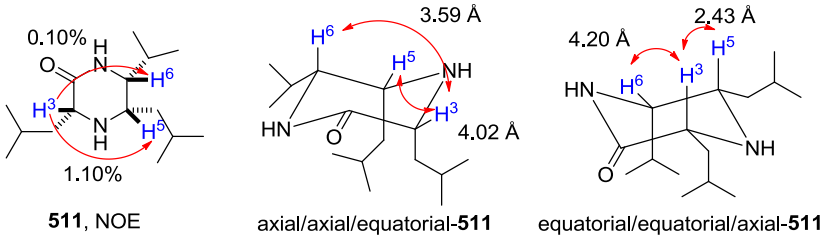
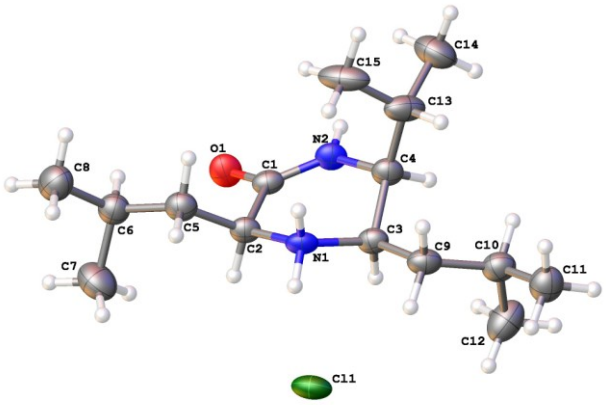
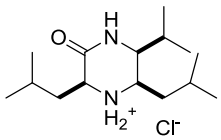


Figure 39

An X-ray crystal structure was obtained for the hydrochloride salt of piperazinone **511** (**548**), showing a *cis/cis* relative stereochemistry (Figure 40). The crystal structure shows that **511** had indeed the equatorial/equatorial/axial conformation, confirmed by the NOE data.





548

Figure 40. X-ray crystal structure of the hydrochloride salt (±)-**548**

2.6.5 Comparison to natural compound

The novel alkaloid piperazirum, isolated from the flowering plant *Arum Palaestinum* by Kim and co-workers was characterised based on a combination of spectroscopic techniques.[224] The compound was isolated as an amorphous white solid, which was judged by mass spectroscopy (ESI) to have a molecular formula of $C_{15}H_{30}N_2O$. IR spectroscopy revealed characteristic absorptions of the NH and C=O groups. ^{1}H NMR spectroscopy in DMSO-d_6 identified the presence of two isobutyl groups in different environments, one isopropyl group, three protons in the region δ 3.4-3.6 ppm, as well as two broad signals at δ 8.45 and 9.45 ppm that were exchangeable with D_2O. Furthermore, ^{13}C NMR showed the presence of fifteen carbon resonances whereas HSQC, HMBS and NOESY were used to completely assign the spectrum of piperazirum. The authors claimed that the observed NOE cross-peaks between protons H^3 and H^5, and H^5 and H^6 show that the three protons are on the same side of the piperazine ring, however no values for the observed NOEs were reported.

Comparison of the reported values of the ^{1}H and ^{13}C NMR resonances showed that these do not match the values for our synthesised compound. The authors obtained the ^{13}C NMR in D_2O but in this case that was only possible for the HCl salt of **511** as the free amine was insoluble. However, the free amine was soluble in DMSO-d_6 and $CDCl_3$ so the ^{13}C resonances were recorded in all those solvents (Table 22). The values of chemical shifts in the ^{13}C NMR for the three ring protons (C^3, C^5 and C^6) were very close in all solvents, so a conclusion could not be drawn from those. However, a significant difference was observed for the chemical shifts of the methylene carbon atoms (CH_2), which were reported to have a difference of 15.4 ppm

in chemical shift for *piperazirum*, but were much closer to each other in our synthesised molecule.

Table 22. ^{13}C NMR chemical shifts of **511** and *piperazirum*

Carbon	δ_C (ppm) $CDCl_3$	δ_C (ppm) DMSO-d_6	δ_C (ppm) D_2O[a]	δ_C (ppm) D_2O[b]
C^2	174.3	172.5	169.9	175.7
C^3	56.9	56.4	54.9	53.6
C^5	53.3	53.2	53.9	59.7
C^6	59.4	58.1	56.3	60.6
CH_2C^3	41.1	41.5	38.8	40.0
CH_2C^5	40.5	40.2	36.3	24.6

[a]Data obtained for the HCl salt of **511**. [b]Reported data for *piperazirum*.

A significant difference was also observed in the ^{1}H NMR spectra. The authors initially obtained the ^{1}H NMR spectra in DMSO-d_6, however the full data they reported were in D_2O. The authors reported the presence of two broad signals at δ 8.45 and 9.45 ppm in DMSO-d_6 corresponding to N*H* protons. However, in our synthesised molecule only one broad peak was observed in the ^{1}H NMR in DMSO-d_6 at δ 6.22 ppm.

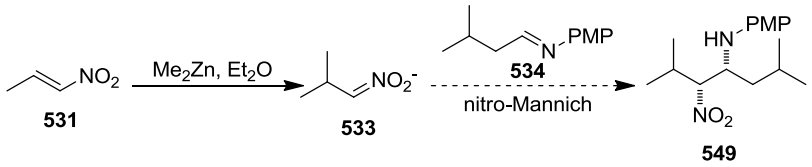
After communication with the authors, it was unsuccessful to obtain a sample of the isolated natural compound or any of the spectra to compare to. In light of these results, it can be tentatively concluded that the reported structure for *piperazirum* was wrongly assigned.

2.6.6 Synthesis of other analogues

After the discovery that the biologically active *piperazirum* isolated from *Arum Palaestinum* did not have the relative stereochemistry claimed by the authors, it was attempted to investigate some other possible structures. As the mass spec and NMR data strongly suggested that the molecular formula and carbon connectivity of the

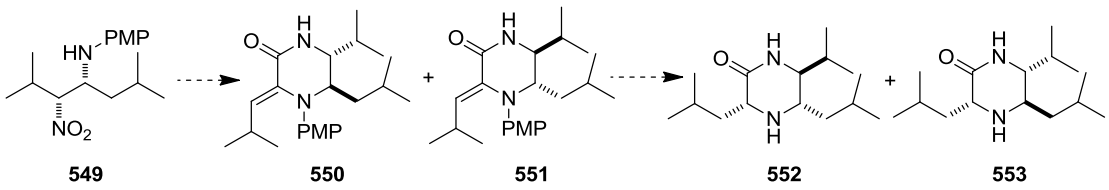
isolated compound was correctly assigned, it can only be assumed that the isolated molecule has a different relative stereochemistry from **511**.

It was thought that access to some other isomers of **511** would be possible using the nitro-Mannich methodology. The *syn* selective nitro-Mannich reaction of dialkylzinc reagents with nitroalkenes has been reported by the Anderson group.[35] This result was observed when Et_2O was used as the reaction solvent causing $Zn(O_2CCF_3)_2$ to precipitate from the solution, which was assumed to change the transition state to an acyclic one instead of cyclic. It was proved that *syn*-*β*-nitroamines **230b** were the thermodynamic products in this reaction (Scheme 78, section 2.1). Therefore a possible route to *syn*-*β*-nitroamine **549** would be the conjugate addition of dimethylzinc to nitroalkene **531** in Et_2O and subsequent nitro-Mannich reaction with imine **534** (Scheme 192).



Scheme 192. Possible route to *syn*-*β*-nitroamine **549**

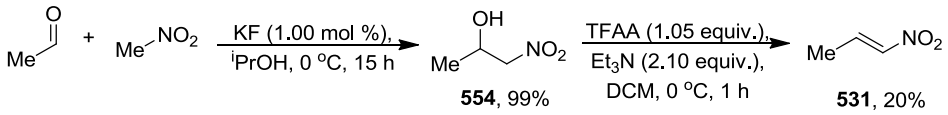
Reduction of *syn*-*β*-nitroamine **549** and lactamisation with ketoacid **519** should give 5,6-dihydropyrazin-2-ones **550** and **551**, that after hydrogenation and deprotection would yield the diastereoisomers **552** and **553** (Scheme 193).



Scheme 193. Possible route to piperazinones **552** and **553**

Nitroalkene **531** was synthesised in two steps from acetaldehyde and nitromethane in 20% overall yield *via* nitroalcohol **554** (Scheme 194).[190] However, brief attempts to access *β*-nitroamine **549** were unsuccessful. Reaction of nitroalkene **531** with dimethylzinc gave only a complicated mixture of products, with only a trace of the desired *β*-nitroamine **549** observed by ^{1}H NMR. This failure can be attributed to the possible instability of imine **534** in these reaction conditions, as no recovered imine or

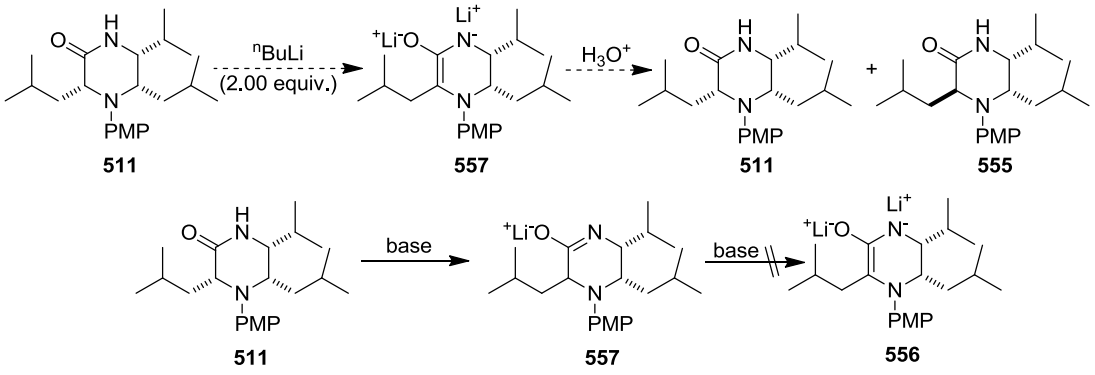
para-anisidine were observed in the crude product mixture, suggesting possible polymerisation *via* initial tautomerisation to enamine.



Scheme 194. Synthesis of nitroalkene **531**

Finally, it was attempted to synthesise diastereoisomer **555** from the already formed piperazine **511**, by epimerisation of the C^3 stereocentre. Double deprotonation of **511** with ^{n}BuLi should give enolate **556**, which after protonation could lead to a mixture of piperazinones **511** and **555** (Scheme 195). However, treatment of **511** with either ^{n}BuLi (2.00 equiv.) or LDA (2.00 equiv.), followed by protonation with water, gave only the starting material **511** and none of the *trans/cis* diastereoisomer **555**.

To explain the above results some deuteration experiments were attempted. Treatment of **511** with either ^{n}BuLi (3.00 equiv.) at THF, at -78 °C to 0 °C or with NaH (5.00 equiv.) at rt, followed by a D_2O quench, led only to deuteration of the amide proton. This result could be expected as initial deprotonation of the amide proton to give enolate **557** would make the proton H^3 much less acidic, making a second deprotonation to **556** more difficult (Scheme 195).



Scheme 195. Epimerisation of piperazinone **511**

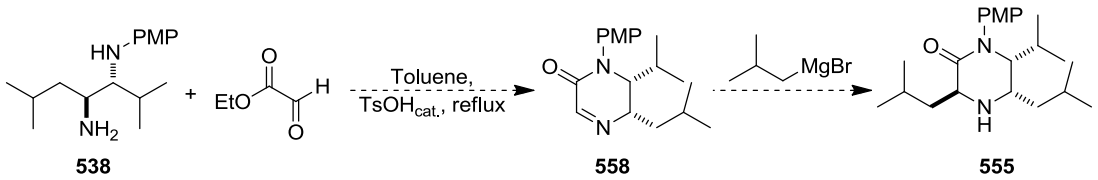
In light of the failure of epimerisation under basic conditions, it was attempted to epimerize **511** by treatment with acid. Refluxing a solution of **511** in toluene with TsOH (5.00 mol %) for 12 h though, gave only recovered starting material as well as some degradation products.

2.6.7 Conclusions and future work

This section described the work done towards the synthesis of natural product *piperazirum*. The reported structure of piperazinone **511** was successfully synthesised using the conjugate addition/nitro-Mannich reaction of Superhydride® with nitroalkene **530** and imine **534**. The desired compound was synthesised in five steps with a 25% overall yield, however the NMR data did not match those of the reported compound, suggesting a wrong assignment of the relative stereochemistry in the natural compound.

Initial attempts to synthesise any other diastereoisomers of **511**, either by epimerisation of the C^3 substituent in **511** or by synthesising piperazinones **552** and **553** *via syn-β*-nitroamine **549** were unsuccessful. This investigation was not continued due to time restrictions, however a more in-depth investigation of the reaction conditions could provide a route to these compounds.

A different route could also give access to piperazinone **555**. Lactamisation of 1,2-diamine **538**, formed earlier in this investigation with ethyl glyoxylate, should give 5,6-dihydropyrazin-2-one **558**. Subsequent reaction of **558** with a suitable Grignard reagent such as ^{i}BuMgBr should lead to nucleophilic addition on the imine group at the C^3 position. It would be expected that the addition of the reagent would occur from the least hindered upper side to give the desired piperazinone **555** (Scheme 196).



Scheme 196. Possible route to piperazinone **555**

Furthermore, after the correct structure of *piperazirum* is identified, the assignment of the absolute stereochemistry and the development of an asymmetric synthesis would be required. A possible asymmetric synthesis of **511** could use organocatalysis to afford the conjugate addition of hydride and asymmetric nitro-Mannich reaction with imine **534**. Thiourea organocatalysts have been used to affect the asymmetric nitro-Mannich reaction, giving high enantioselectivities and good yields.[122]

3. Experimental

3.1 General experimental details

All non-aqueous chemistry, unless otherwise stated, was carried out in flame dried glassware, under an inert atmosphere (anhydrous N_2), using a Schlenk apparatus. Room temperature implies the temperature range of 20-25 ^oC. All reaction temperatures stated refer to the values of the external bath and not the reaction mixture. An ice-water bath was used for cooling at 0 ^oC, whereas cryogenic conditions (-78 ^oC and -25 ^oC) were accomplished using an acetone/dry-ice bath. Reagents were added into the reaction mixture fast (solution or liquid) and in one portion (solid), unless otherwise stated. Column chromatography was performed using Geduran® silica gel 60, 40-63 μm in the indicated solvent system. Thin layer chromatography (TLC) was used for monitoring both reactions and the progress of column chromatography and was performed on Polygram® SIL G/UV254 0.25 mm silica pre coated aluminium plates with fluorescent indicator, which were then visualised under UV light (254 nm) and a dip of basic potassium permanganate. Removal of solvents (*in vacuo*) was achieved using the house vacuum system and Büchi rotary evaporators. Pyrrolidinones **231** (racemic), **238**, **240**, **246** and **242** were made according to the reported procedure.[119] Compounds **353**,[173] **370**,[175] **519**,[226] **520**,[225] **523**,[228] **530**,[232] and **531**,[189] were made according to the reported procedures. Imines **261** and **262** were provided by colleague Paul Koovits.[122] Thiazole-2-carboxaldehyde,[236] oxazole-2-carboxaldehyde,[237] and (±)-3,3'-dimethyl-[1,1'-binaphthalene]-2,2'-diol,[131] were made according to the reported procedures. Where the described compound is made by a literature procedure not used to make the specific compound before, this is referenced in the compound name.

3.2 Purification of solvents and reagents

Commercial solvents and reagents were used as supplied or purified in accordance to standard procedures.[238] The dry solvents Diethyl Ether (Et_2O), Tetrahydrofuran (THF), Dichloromethane (DCM), Toluene and Hexane were obtained from a solvent tower, where degassed solvents were passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure. All commercial reagents were used as supplied without further purification, unless otherwise stated. All amines, anilines, pyridines and phenols were distilled or recrystallised according to literature

procedures.[238] Benzaldehyde was distilled from calcium hydride under an atmosphere of nitrogen, and stored at 5 ^{o}C. Diethylzinc was purchased from Aldrich as a 1.0 M solution in hexanes and stored under Nitrogen. Diisopropylzinc was synthesised according to a literature procedure,[126] as a solution in hexane, titrated with I_2/LiCl,[125] and stored under Nitrogen at -20 ^{o}C. Diphenylzinc was purchased from Aldrich as a white solid and stored in an inert atmosphere box. Superhydride® was purchased from Aldrich as a 1.0 M solution in THF and stored under Nitrogen. Copper (II) triflate was stored in an inert atmosphere box and used immediately after being weighed out. All solutions of organolithium reagents were kept under a Nitrogen atmosphere at 5 ^{o}C and standardised with Salicylaldehyde Phenylhydrazone.[239] Activation of 4 Å molecular sieves was achieved by heating under high vacuum.

3.3 Characterisation

Melting points are uncorrected and were recorded on a Reichert Melting Point Apparatus. All ^{1}H and ^{13}C NMR data were recorded using Bruker AVANCE III 400 MHz and Bruker AVANCE III 600 MHz machines at 400 and 600 MHz for ^{1}H and 100 and 125 MHz for ^{13}C respectively. ^{19}F NMR data were recorded on a Bruker AMX 300 MHz machine at 282 MHz. Samples were made as dilute solutions of $CDCl_3$ and spectra recorded at 298 K, unless otherwise stated. Data were manipulated directly using Bruker XwinNMR (version 2.6) or TopSpin (version 2.1). All chemical shifts (δ) are reported in parts per million (ppm), relative to residual solvent peaks δ = 7.26 for ^{1}H NMR and δ = 77.1 for ^{13}C NMR. Multiplicities for ^{1}H coupled signals are denoted as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet. Coupling constants (*J*) are reported in Hertz (Hz). ^{13}C multiplicities were assigned using a DEPT sequence. Where appropriate, HMQC, COSY, HMBC, NOE experiments were carried out to aid assignment. Mass spectroscopy data were collected on Thermo Finnigan Mat900xp (EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Infrared data were collected using Perkin-Elmer 100 FTIR spectrometer as a thin film. Elemental analysis was performed on an Exeter Analytical Inc. EA440 horizontal load analyser. Optical rotations were obtained using a Perkin-Elmer 343 model polarimeter. X-ray crystallography was carried out using a AFC12 goniometer, equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100μm focus).

3.4 Experimental procedures

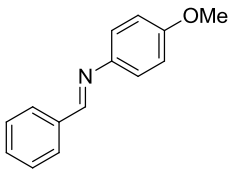
3.4.1 Stereoselective synthesis of pyrrolidinones *via* nitro-Mannich reaction

3.4.1.1 Preparation of imines, nitroalkenes and other starting materials

General Procedure A: Synthesis of PMP imines

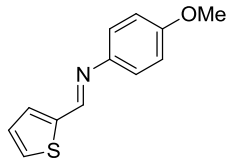
To a solution of *para*-anisidine (1.0 mmol) in DCM (5 mL per mmol) was added basic Al_2O_3 (1.0 g per mmol) and the mixture stirred at rt for 5 min. Aldehyde (1.00 mmol) was then added and the mixture stirred for a further 15 h before being filtered through celite® and washed with DCM (5 mL per mmol). The filtrate was concentrated *in vacuo* to give crude imine.

(*E*)-*N*-benzylidene-4-methoxyaniline 281



Prepared by general procedure A. Benzaldehyde (3.00 mL, 30 mmol), *para*-anisidine (3.69 g, 30.0 mmol) and basic Al_2O_3 (30.0 g) afforded imine **281** (6.23 g, 95% pure by ^{1}H NMR, 98%,) as a yellow solid which was used without further purification; mp. 71-72 ^{o}C (lit. 70-71 ^{o}C); ^{1}H NMR (600 MHz) δ 3.85 (3H, s, OCH_3), 6.95 (2H, app. d, J = 8.8, C$H_{PMPC3\text{-}H}$), 7.26 (2H, app. d, J = 8.8, C$H_{PMPC2\text{-}H}$), 7.48 (3H, m, C*H* Arom.), 7.91 (2H, m, C*H* Arom.), 8.50 (1H, s, N=C*H*). Data in agreement with that reported.[240]

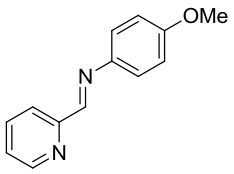
(*E*)-4-methoxy-*N*-(thiophen-2-ylmethylene)aniline 558



Prepared by general procedure A. 2-Thiophene carboxaldehyde (2.80 mL, 30.0 mmol), *para*-anisidine (3.69 g, 30.0 mmol) and basic Al_2O_3 (30.0 g) afforded imine

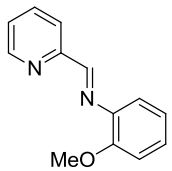
558 (6.38 g, 98% pure by ^{1}H NMR, 100%,) as a yellow solid which was used without further purification; mp. 46-47 ^{o}C (lit. 47-48 ^{o}C); ^{1}H NMR (600 MHz) δ 3.84 (3H, s, OCH_3), 6.93 (2H, app. d, J = 8.8, C$H_{PMPC3-H}$), 7.13 (1H, m, C$H_{thiophene}$), 7.24 (2H, app. d, J = 8.8, C$H_{PMPC2-H}$), 7.48 (2H, m, C$H_{thiophene}$), 9.96 (1H, s, N=CH). Data in agreement with that reported.[241]

(*E*)-4-methoxy-*N*-(pyridin-2-ylmethylene)aniline 256



Prepared by general procedure A. 2-Pyridinecarboxaldehyde (0.950 mL, 10.0 mmol), *para*-anisidine (1.23 g, 10.0 mmol) and basic Al_2O_3 (10.0 g), afforded imine **256** (1.93 mg, 91%) as a white solid which was used without further purification; mp. 34-35 ^{o}C (36-37 ^{o}C); ^{1}H NMR (600 MHz) δ 3.85 (3H, s, OCH_3), 6.96 (2H, app. d, J = 8.8, C$H_{PMPC3-H}$), 7.35 (3H, m, C$H_{PMPC2-H}$ and C$H_{pyridine}$), 7.80 (1H, m, C$H_{pyridine}$), 8.19 (1H, d, J = 8.1, C$H_{pyridine}$), 8.64 (1H, s, CHN), 8.71 (1H, m, C$H_{pyridine}$). Data in agreement with that reported.[242]

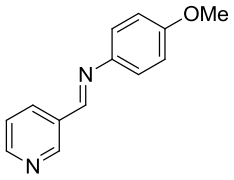
(*E*)-2-methoxy-*N*-(pyridin-2-ylmethylene)aniline 559



To a solution of *ortho*-anisidine (1.13 mL, 10.0 mmol) in DCM (50 mL) were added dry molecular sieves 4 Å (10.0 g) and the mixture stirred at rt for 5 min. 2-Pyridinecarboxaldehyde (0.95 mL, 10.0 mmol) was then added and the mixture stirred for a further 6 h before being filtered through celite® and washed with DCM (50 mL). The filtrate was concentrated *in vacuo* to give crude imine **559** (1.93 mg, 80% pure by NMR, 91%,) as a yellow solid which was used without further purification; ^{1}H NMR (600 MHz) δ 3.92 (3H, s, OCH_3), 7.00 (2H, m, CH Arom.), 7.11 (1H, m, CH Arom.),

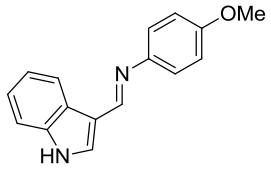
7.24 (1H, m, C*H* Arom.), 7.38 (1H, m, C*H* Arom.), 7.83 (1H, m, C*H* Arom.), 8.29 (1H, m, C*H* Arom.), 8.65 (1H, s, N=C*H*), 8.71 (1H, m, C*H* Arom.). Data in agreement with that reported.[243]

(*E*)-4-methoxy-*N*-(pyridin-3-ylmethylene)aniline 257



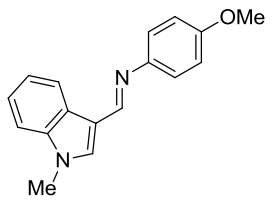
Prepared by general procedure A. 3-Pyridinecarboxaldehyde (2.82 mL, 30.0 mmol), *para*-anisidine (3.69 g, 30.0 mmol) and basic Al_2O_3 (30.0 g) afforded crude imine **257** (5.87 g, 93%), recrystallised from Et_2O/Petrol (4.61 g, 73%) as a white solid; mp. 56-57 ^oC; ^1H NMR (600 MHz) δ 3.81 (3H, s, OCH_3), 6.97 (2H, app. d, J = 8.9, C$H_{PMPC3-H}$), 7.28 (2H, app. d, J = 8.9, C$H_{PMPC3-H}$), 7.41 (1H, m, C$H_{pyridine}$), 8.28 (1H, m, C$H_{pyridine}$), 8.54 (1H, s, N=C*H*), 8.69 (1H, m, C$H_{pyridine}$), 9.0 (1H, m, C$H_{pyridine}$). Data in agreement with that reported.[244]

(*E*)-*N*-((1*H*-indol-3-yl)methylene)-4-methoxyaniline 258



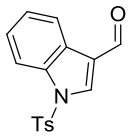
Prepared by general procedure A. Indole-3carboxaldehyde (1,45 g, 10.0 mmol), *para*-anisidine (1.23 g, 10.0 mmol) and basic Al_2O_3 (10.0 g) afforded imine **258** (2.38 g, 95%, lit. 98%) as a yellow solid which was used without further purification; mp. 116-118 ^oC (lit. 115-120 ^oC); ^1H NMR (600 MHz) δ 3.84 (3H, s, OCH_3), 6.93 (2H, app. d, J = 8.8, C$H_{PMPC3-H}$), 7.24 (1H, m, CH_{indole}), 7.28 (2H, app. d, J = 8.8, C$H_{PMPC2-H}$), 7.40 (1H, m, CH_{indole}), 7.62 (1H, s, N=C*H*), 8.51 (1H, m, CH_{indole}), 8.68 (1H, br. s, N*H*), 8.71 (1H, s, CH_{indole}). Data in agreement with that reported.[245]

(*E*)-4-methoxy-*N*-((1-methyl-1*H*-indol-3-yl)methylene)aniline 259



To a solution of imine **258** (1.25 g, 5.00 mmol) in THF (15 mL), cooled to 0 °C was added NaH (151 mg, 6.00 mmol, 95%) and the mixture stirred for 15 min, then 1 h at rt. The mixture was then recooled to 0 °C and MeI (0.37 mL, 6.00 mmol) was added, the mixture warmed to rt and stirred for 30 min. Water (20 mL) was then added and the mixture extracted with DCM (3x20 mL), dried over $MgSO_4$ and evaporated *in vacuo* to afford imine **259** (1.23 g, 93%) as a yellow oil which was used without further purification; ^{1}H NMR (600 MHz) δ 3.82 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 6.95 (2H, app. d, J = 8.8, C$H_{PMPC3-H}$), 7.25 (2H, app. d, J = 8.8, C$H_{PMPC2-H}$), 7.31 (1H, m, CH_{indole}), 7.36 (2H, m, CH_{indole}), 7.49 (1H, m, CH_{indole}), 8.50 (1H, m, CH_{indole}), 8.65 (1H, s, N=C*H*). Data in agreement with that reported.[246]

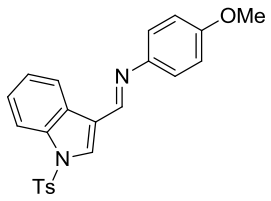
1-Tosyl-1*H*-indole-3-carbaldehyde 560



A solution of indole-3-aldehyde (500 mg, 3.40 mmol) in DCM (7 mL) was cooled to 0 °C and then *para*-toluenesulfonyl chloride (730 mg, 3.80 mmol) was added followed by Et_3N (470 µL, 3.80 mmol) and the mixture left to warm to rt and stirred overnight until the starting aldehyde was consumed (TLC, 20 h). Saturated aqueous $NaHCO_3$ (10 mL) was then added, the layers separated and aqueous layer further extracted with DCM (2x10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude aldehyde **560**. Purification by flash column chromatography (Hexane:DCM 1:1) gave aldehyde **560** (776 mg, 76%) as a yellow solid; mp. 141-143 °C (lit. 143-144 °C); Rf = 0.41 (Hexane:DCM 1:1); ^{1}H NMR (600 MHz) δ 2.38 (3H, s, ArCH_3), 7.29 (2H, d, J = 8.2, CH_{TsC3-H}), 7.37 (1H, m, CH_{indole}), 7.42 (2H, m, CH_{indole}), 7.86 (2H, d, J = 8.4, CH_{TsC2-H}), 7.96 (1H, d, J = 8.3, CH_{indole}), 8.24 (1H, s, C$H_{indoleC2-H}$), 8.26 (1H,

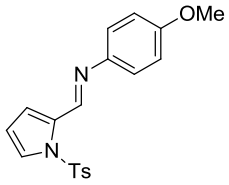
d, J = 8.0, CH_{indole}), 10.11 (1H, s, O=CH); ^{13}C NMR (150 MHz) δ 21.8 (CH_3), 113.4 (CH Arom.), 122.5 (Cq Arom.), 122.7 (CH Arom.), 125.2 (CH Arom.), 126.3 (Cq Arom.), 126.4 (CH Arom.), 127.4 (CH Arom.), 130.5 (CH Arom.), 134.4 (Cq Arom.), 135.3 (Cq Arom.), 136.4 (CH Arom.), 146.4 (Cq Arom.), 185.7 (HC=O). Data in agreement with that reported.[247]

(*E*)-4-methoxy-*N*-((1-tosyl-1*H*-indol-3-yl)methylene)aniline 260



Prepared by general procedure A. Aldehyde **560** (4.61 g, 15.4 mmol), *para*-anisidine (1.90 g, 15.4 mmol) and basic Al_2O_3 (15.0 g) afforded imine **260** (5.40 g, 89%) as a brown solid which was used without further purification; mp. 90-92 °C; ^{1}H NMR (600 MHz) δ 2.36 (3H, s, ArCH_3), 3.85 (3H, s, OCH_3), 6.95 (2H, d, J = 9.0, C$H_{PMPC3-H}$), 7.25 (4H, m, CH Arom.), 7.36 (2H, m, CH Arom.), 7.82 (2H, d, J = 8.4, CH Arom.), 7.98 (1H, s, CH Arom.), 8.00 (1H, m, CH Arom.), 8.54 (1H, m, CH Arom.), 8.63 (1H, s, N=CH). Data in agreement with that reported.[248]

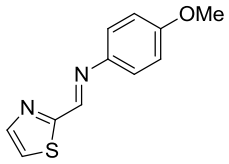
(*E*)-4-methoxy-*N*-((1-tosyl-1*H*-pyrrol-2-yl)methylene)aniline 263



To a solution of imine **261** (380 mg, 1.90 mmol) in THF (10 mL) cooled to 0 ^{o}C was added NaH (46 mg, 1.9 mmol, 95%) and the mixture stirred for 15 min, then 30 min at rt. The mixture was then cooled to 0 ^{o}C and *para*-toluenesulfonyl chloride (362 mg, 1.90 mmol) was added, the mixture warmed to rt and stirred for 30 min. Water (20 mL) was then added and the mixture extracted with DCM (3x20 mL), dried over $MgSO_4$ and evaporated *in vacuo* to afford imine **263** (654 mg, 97%) as a yellow oil which was used without further purification; mp. 74-75 ^{o}C; IR υ_{max} (thin film) 2834 w

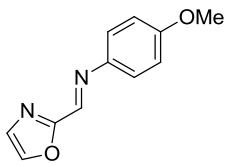
(C-H), 1614 m (C=C), 1494 m, 1373 m, 1362 m, 1251 m, 1165 s, 1130 s, 1050 s, 813 s, 726 s, 671 s cm-1; ^{1}H NMR (600 MHz) δ 2.38 (3H, s, ArCH_3), 3.83 (3H, s, OCH_3), 6.38 (1H, m, C$H_{pyrrole}$), 6.92 (2H, app. d, J = 8.8, C$H_{PMPC3-H}$), 7.10 (1H, m, C$H_{pyrrole}$), 7.18 (2H, app. d, J = 8.8, C$H_{PMPC2-H}$), 7.27 (2H, app. d, J = 8.3, C$H_{tosylC3-H}$), 7.46 (1H, m, C$H_{pyrrole}$), 7.68 (2H, app. d, J = 8.3, C$H_{tosylC2-H}$), 8.89 (1H, s, N=CH); ^{13}C NMR (150 MHz) δ 21.6 (ArCH$_3$), 55.5 (OCH$_3$), 113.1 (*C*H Arom.), 114.4 (*C*H Arom.), 116.9 (*C*H Arom.), 122.3 (*C*H Arom.), 126.1 (*C*H Arom.), 126.8 (*C*H Arom.), 130.1 (*C*H Arom.), 133.1 (*C*q Arom.), 135.8 (*C*q Arom.), 144.6 (*C*q Arom.), 145.5 (*C*q Arom.), 147.5 (N=*C*H), 158.4 (*C*q$_{PMPC3}$); *m/z* (ESI$^+$) 355 (M+H$^+$, 32%), 347 (24%), 199 (100%); HRMS: found 355.1111, $C_{19}H_{19}N_2O_3S$ requires 355.1116; Anal. Cald. for $C_{19}H_{18}N_2O_3S$: C, 64.34, H, 5.12, N, 7.90. Found C, 64.17, H, 5.09, N, 7.85%.

(*E*)-4-methoxy-*N*-(thiazol-2-ylmethylene)aniline 264



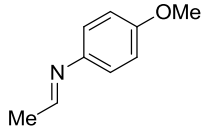
To a solution of *para*-anisidine (1.26 g, 10.0 mmol) in DCM (40 mL), was added anhydrous $MgSO_4$ (10.0 g) followed by thiazole-2-carboxaldehyde (1.16 g, 10.3 mmol) and the mixture was then stirred at rt for 2 h. The mixture was then filtered and evaporated *in vacuo* to give crude imine **264** (2.06 g, 92%) as a yellow solid which was recrystallised from Et_2O/hexane (1.11 g, 50%); mp. 64-66 ^{o}C; IR υ_{max} (thin film) 3008 w (C-H), 2961 w (C-H), 1615 s (C=C), 1504 s, 1410 m, 1291 s, 1247 s, 1237 s, 1166 s, 1028 s, 837 s, 785 s, 739 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.86 (3H, s, OCH_3), 6.96 (2H, d, J = 8.7, C$H_{PMPC3-H}$), 7.35 (2H, d, J = 8.7, C$H_{PMPC4-H}$), 7.48 (1H, d, J = 3.0, C$H_{thiazoleC5-H}$), 7.99 (1H, d, J = 3.0, C$H_{thiazoleC4-H}$), 8.73 (1H, s, N=CH); ^{13}C NMR (150 MHz) δ 55.6 (OCH$_3$), 114.6 (*C*H$_{PMPC3}$), 122.0 (*C*H$_{thiazoleC4}$), 123.0 (*C*H$_{PMPC2}$), 142.7 (*C*q$_{PMPC1}$), 144.5 (*C*H$_{thiazoleC3}$), 150.6 (*C*q$_{thiazoleC2}$), 159.5 (*C*q$_{PMPC4}$), 167.9 (H*C*=N); *m/z* (ESI$^+$) 219 (M + H, 100%), 218 (18%); HRMS: found 219.0596 $C_{11}H_{11}N_2OS$ requires 219.0992; Anal. Cald. for $C_{11}H_{10}N_2OS$: C, 60.53, H, 4.92, N, 12.83. Found C, 60.59, H, 4.53, N, 12.70%.

(*E*)-4-methoxy-*N*-(oxazol-2-ylmethylene)aniline 265



To a solution of *para*-anisidine (492 mg, 4.00 mmol) in DCM (40 mL), was added anhydrous $MgSO_4$ (5.00 g) followed by oxazole-2-carboxaldehyde (400 mg, 4.11 mmol) and the mixture was then stirred at rt for 19 h. The mixture was then filtered and evaporated *in vacuo* to give crude imine **265** (1.22 g, 70% pure by ^{1}H NMR, 85%), recrystallised from Et_2O/petrol (664 mg, 80%) as white needles which was used without further purification; mp. 92-93 °C; IR υ_{max} (thin film) 3119 w (C-H), 2954 w (C-H), 1628 m (C=C), 1591 m, 1540 m, 1507 s, 1493 s, 1294 s, 1031 m, 915 m cm^{-1}; ^{1}H NMR (600 MHz) δ 3.86 (3H, s, OC*H*$_3$), 6.97 (2H, d, *J* = 9.1, C*H*$_{PMPC3-H}$), 7.37 (1H, s, C*H*$_{oxazoleC4-H}$), 7.39 (2H, d, *J* = 9.1, C*H*$_{PMPC3-H}$), 7.82 (1H, s, C*H*$_{oxazoleC5-H}$), 8.47 (1H, s, N=C*H*); ^{13}C NMR (150 MHz) δ 55.5 (O*C*H$_3$), 114.6 (*C*H$_{PMPC3}$), 123.0 (*C*H$_{PMPC2}$), 129.4 (*C*H$_{oxazoleC4}$), 140.4 (*C*H$_{oxazoleC5}$), 142.4 (*C*q$_{PMPC1}$), 143.3 (*C*q$_{oxazoleC2}$), 159.8 (*C*q$_{PMPC4}$), 162.4 (N=*C*-H); *m/z* (ES$^+$) 202 (M$^+$, 75%), 187 (32%, M$^+$- CH$_3$), 134 (62%, M$^+$- oxazole), 98 (100%); HRMS: found 202.0732, $C_{11}H_{10}N_2O_2$ requires 202.0737; Anal. Cald. For $C_{11}H_{10}N_2O_2$: C, 65.34, H, 4.98, N, 13.85. Found C, 65.17, H, 4.88, N, 13.83%.

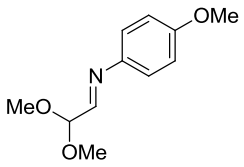
(*E*)-*N*-ethylidene-4-methoxyaniline 266



To a solution of *para*-anisidine (123 mg, 1.00 mmol) in DCM (5 mL), was added basic Al_2O_3 (1.00 g) and the mixture cooled to -78 °C. Acetaldehyde (67 μL, 1.2 mmol) was then added and the mixture stirred at this temperature for 1 h, then warmed to rt, filtered through celite® and evaporated *in vacuo* to give crude imine **266** (145 mg, 97%) as a colourless oil which was used immediately without further purification; IR υ_{max} (thin film) 2997 w (C-H), 1651 m (C=O), 1605 m, 1502 s, 1464 m, 1441 m, 1292 m, 1238 s, 1210 m, 1032 s, 819 s, 749 m, 714 m cm^{-1}; ^{1}H NMR (600

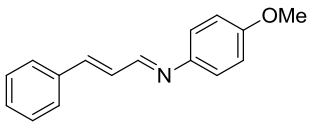
MHz) δ 2.17 (3H, d, *J* = 5.0, C*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 6.87 (2H, app. d, *J* = 8.8, C*H*$_{PMPC3-H}$), 7.02 (2H, app. d, *J* = 8.8, C*H*$_{PMPC2-H}$), 7.91 (1H, q, *J* = 5.0, N=C*H*); ^{13}C NMR (150 MHz) δ 23.0 (*C*H$_3$), 55.4 (O*C*H$_3$), 114.2 (*C*H$_{PMPC3}$), 121.7 (*C*H$_{PMPC2}$), 145.1 (*C*q$_{PMPC1}$), 157.7 (*C*q$_{PMPC4}$), 160.6 (N=*C*H); *m/z* (CI$^+$) 150 (95%, M$^+$), 123 (100%, *para*-anisidine$^+$); HRMS: found 150.091101, $C_9H_{11}NO$ requires 150.09188.

(*E*)-*N*-(2,2-dimethoxyethylidene)-4-methoxyaniline 267



Prepared according to the reported procedure.[249] To a solution of *para*-anisidine (3.69 g, 30.0 mmol) in DCM (120 mL), was added anhydrous $MgSO_4$ (25.0 g) followed by 2,2-dimethoxyacetaldehyde (5.87 mL, 60% in H_2O, 39.0 mmol) and the mixture was stirred at rt for 2 h. The mixture was then filtered and evaporated *in vacuo* to give imine **267** (6.14 g, 98%, lit. 97%) as a colourless oil which was used without further purification; ^{1}H NMR (600 MHz) δ 3.48 (6H, s, OC*H*$_3$), 3.81 (3H, s, ArOC*H*$_3$), 4.89 (1H, d, J = 4.3, C*H*(OCH$_3$)$_2$), 6.89 (2H, app. d, *J* = 8.8, C*H* Arom.), 7.16 (2H, app. d, *J* = 8.8, C*H* Arom.), 7.74 (1H, d, *J* = 4.2, =C*H*). Data in agreement with that reported.[249]

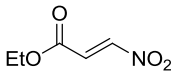
(*E*)-4-Methoxy-*N*-((*E*)-3-phenylallylidene)aniline 268



To a solution of *para*-anisidine (1.84 g, 15.0 mmol) in DCM (75 mL), was added anhydrous $MgSO_4$ (15.0 g) followed by cinnamaldehyde (1.90 mL, 15.0 mmol) and the mixture was stirred at rt for 2 h. The mixture was then filtered and evaporated *in vacuo* to give imine **268** (3.47 g, 98%) as a white solid which was used without further purification; mp. 117-118 ^{o}C (lit. 119-120 ^{o}C); ^{1}H NMR (600 MHz) δ 3.84 (3H, s, OC*H*$_3$), 6.94 (2H, app. d, *J* = 9.0, C*H*$_{PMPC3}$), 7.14 (2H, m, PhC*H* and

PhCH=C*H*), 7.23 (2H, app. d, *J* = 9.0, CH_{PMPC2}), 7.36 (1H, m, C*H* Arom.), 7.41 (2H, m, C*H* Arom.), 7.55 (1H, m, C*H* Arom.), 8.81 (1H, s, N=C*H*). Data in agreement with that reported.[250]

(*E*)-ethyl 3-nitroacrylate 231

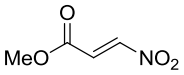


The compound was synthesised by a modification of the reported procedure.[121] In a 25 mL round bottom flask was added ethyl glyoxylate (4.08 g of a 50% solution in toluene, 20.0 mmol) followed by nitromethane (8 mL) and basic Al_2O_3 (4.00 g). The mixture was stirred at rt for 4 days before being filtered and concentrated *in vacuo* to give crude nitroalcohol **255** (1.99 g, 61% yield) as a yellow oil; R_f 0.23 (Petrol:EtOAc 1:1) used without further purification. To a solution of crude nitroalcohol **255** (1.99 g, 12.2 mmol) in DCM (35 mL) at –25 °C was added methanesulfonyl chloride (2.83 mL, 36.6 mmol) followed by Et_3N (5.10 mL, 36.6 mmol) dropwise. The mixture was stirred at –25 °C until complete consumption of the nitroalcohol starting material (TLC, 20 min). The reaction mixture was then poured into ice (30 g) and the layers separated. The aqueous phase was extracted with DCM (2x20 mL) and the combined organics washed with saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroacrylate **231** (1.28 g, 72%, 44% over two steps, lit. 77%) as a low melting yellow solid; mp. 36-37 °C (lit. 39-40 °C); R_f 0.37 (Petrol:Et_2O 9:1); ^{1}H NMR (600 MHz) δ 1.36 (3H, t, *J* = 7.1, CH_3), 4.34 (2H, q, *J* = 7.2, CH_2CH$_3$), 7.10 (1H, d, *J* = 13.5, =C*H*CO$_2$Et), 7.69 (1H, d, *J* = 13.5, =C*H*NO$_2$); ^{13}C NMR (150 MHz) δ 14.1 (*C*H$_3$), 62.5 (*C*H$_2$), 127.8 (=*C*HCO), 149.0 (=*C*HNO$_2$), 162.8 (*C*=O). Data in agreement with that reported.[120]

Also prepared by reaction of ethyl acrylate with CAN. To a stirred solution of ethyl acrylate (2.18 mL, 20.0 mmol) in MeCN (28 mL) at 0 ^{o}C were added CAN (32.8 g, 60.0 mmol) followed by $NaNO_2$ (4.14 g, 60.0 mmol) and the mixture was left to warm to rt and stirred for 24 h. Water (20 mL) was then added and the mixture extracted with EtOAc (3x20 mL), then the combined organics washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated *in*

vacuo. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroacrylate **296** (1.99 g, 61%) as a yellow oil, identical to the one described above.

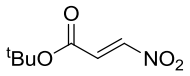
(*E*)-Methyl 3-nitroacrylate 291



The compound was synthesised in three steps according to the reported procedures starting from glyoxylic acid. In a 100 mL round bottom flask was added glyoxylic acid monohydrate (4.20 g, 45.5 mmol) and H_2O (50 mL) and the solution was neutralised by addition of aqueous NaOH 10% until pH = 9. Another 1 mL of the NaOH solution was then added followed by nitromethane (14.6 mL, 270 mmol) and the mixture stirred at rt for 22 h. A 3 M H_2SO_4 solution (100 mL) was then added and the mixture extracted with EtOAc (3x20 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give 2-hydroxy-3-nitropropanoic acid (5.97 g, 97%) as a white solid; mp. 76-77 ^oC (lit. 76-77 ^oC),[251] used without further purification. To a solution of the crude 2-hydroxy-3-nitropropanoic acid (5.97 g, 44.0 mmol) in MeOH (80 mL) was added concentrated H_2SO_4 (0.25 mL, 4.7 mmol) and the mixture was refluxed for 12 h, then neutralised with addition of saturated aqueous $NaHCO_3$, evaporated *in vacuo* to remove MeOH, then extracted with DCM (3 x 20 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude methyl 2-hydroxy-3-nitropropanoate (6.00 g, 94%) as a colourless oil, used without further purification;[134] R_f 0.44 (Petrol:EtOAc 3:2); ^1H NMR (600 MHz) δ 3.30 (1H, d, *J* = 4.8, O*H*), 3.91 (3H, s, OCH_3), 4.67 (1H, q, *J* = 4.3, C*H*CO), 4.79 (2H, dd, *J* = 3.9, 2.5, CH_2NO_2). To a solution of crude methyl 2-hydroxy-3-nitropropanoate (2.06 g, 13.8 mmol) in DCM (25 mL) at -25 °C was added methanesulfonyl chloride (3.20 mL, 41.4 mmol) followed by Et_3N (5.77 mL, 41.4 mmol) dropwise. The mixture was stirred at -25 °C until complete consumption of the nitroalcohol starting material (TLC, 20 min).[120] The reaction mixture was then poured into ice (30 g) and the layers separated. The aqueous phase was extracted with DCM (2x20 mL) and the combined organics washed with saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroacrylate **291** (1.28 g, 72%, 44% over two steps, lit. 77%) as a low melting yellow solid; mp. 36-37 °C (lit. 34-35 °C); R_f 0.33

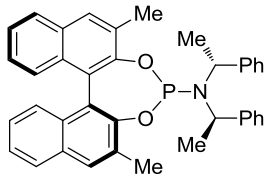
(Petrol:Et_2O 9:1); ^1H NMR (600 MHz) δ 3.89 (3H, s, OCH_3), 7.11 (1H, d, *J* = 13.5, =C*H*CO), 7.70 (1H, d, *J* = 13.5, =C*H*NO_2). Data in agreement with that reported.[252]

(*E*)-*tert*-Butyl 3-nitroacrylate 296



To a stirred solution of *tert*-butyl acrylate (2.90 mL, 20.0 mmol) in MeCN (28 mL) at 0 °C were added CAN (32.8 g, 60.0 mmol) followed by $NaNO_2$ (4.14 g, 60.0 mmol) and the mixture was left to warm to rt and stirred for 24 h. Water (20 mL) was then added and the mixture extracted with EtOAc (3x20 mL), then the combined organics washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroacrylate **296** (331 mg, 10%) as a yellow oil; R_f 0.68 (Petrol:Et_2O 9:1); ^1H NMR (600 MHz) δ 1.54 (9H, s, CH_3), 7.02 (1H, d, *J* = 13.4, =C*H*CO), 7.60 (1H, d, *J* = 13.4, =C*H*NO_2). Data in agreement with that reported.[136]

((*P*)-*Bis*-3,3′-dimethyl-naphthaleno[1,2-f;2,1-d]-1,3-dioxa-2-phosphacycloheptan-2-yl)-(*R,R*)-bis(1-phenylethyl)amine 294



Prepared according to the reported procedure.[130] A solution of (+)-bis(*R*-1-phenylethyl)amine (530 µL, 2.32 mmol) and triethylamine (360 µL, 2.62 mmol) in toluene (2 mL) was added dropwise to a solution of phosphorus trichloride (200 µL, 2.32 mmol) in toluene (30 mL). The mixture was stirred at 70 °C for 6 h and allowed to cool to rt. Triethylamine (720 µL, 5.26 mmol) was then added dropwise and the reaction mixture cooled to -78 °C. A solution of (±)-3,3'-dimethyl-[1,1'-binaphthalene]-2,2'-diol (728 mg, 2.32 mmol) in a mixture of toluene (6 mL) and THF (2 mL) was added dropwise. The mixture was allowed to warm up to rt and stirred for 18 h. The mixture was evaporated *in vacuo* and the diastereomers separated

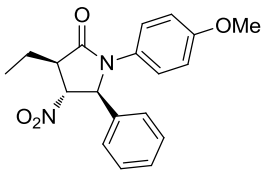
and purified by flash column chromatography (Hexane:DCM 9:1). The desired product **294** was isolated as a white solid (853 mg, 32%, lit. 49%); mp. 117-119 ^{o}C (lit. 116-123 ^{o}C); R_f 0.32 (Hexane:DCM 9:1); ^{1}H NMR (600 MHz) δ 1.70-195 (6H, br. s, CHC*H*$_3$), 2.44 (3H, s, ArC*H*$_3$), 2.76 (3H, s, ArC*H*$_3$), 4.59 (2H, br. s, C*H*), 7.00-7.14 (13H, m, C*H* Arom.), 7.37 (3H, m, C*H* Arom.), 7.83 (4H, m, C*H* Arom.). Data in agreement to the one reported.[130]

3.4.1.2 Preparation of pyrrolidinones

General procedure B for the asymmetric synthesis of pyrrolidinones 233 and 241.

A suspension of Cu(OTf)$_2$ (8 mg, 22 μmol, 5 mol%) and BINOL derived catalyst **294** (15 mg, 27 μmol, 5 mol%) in Et_2O (3 mL) was stirred at rt for 1 h. The mixture was cooled to –78 °C and a solution of methyl nitroacrylate (76 mg, 0.58 mmol) in Et_2O (1 mL) was added, followed by diethylzinc (640 μL, 0.640 mmol of a 1 M sol. in hexanes, 1.1 equiv.) fast dropwise. The now orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. The mixture was re-cooled to –78 °C and the PMP-protected imine (1.16 mmol, 2.0 equiv.) in THF (2 mL) was added *via* cannula. The mixture was stirred for 20 min before TFA (156 μL, 2.03 mmol, 3.5 equiv.) in THF (0.5 mL) was added *via* cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt and stirred for a further 16 h. Saturated aqueous $NaHCO_3$ (20 mL) and Et_2O (20 mL) were then added and the layers separated. The aqueous phase was extracted with Et_2O (3x20 mL) and the combined organics was washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave crude pyrrolidinone.

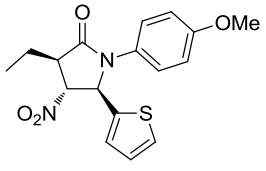
(3*R*, 4*R*, 5*S*)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-phenyl-pyrrolidin-2-one 233



Prepared by general procedure B. Nitroacrylate **291** (76 mg, 0.580 mmol), diethyl zinc (638 µL, 0.638 mmol), imine **281** (245 mg, 1.16 mmol) and TFA (155 µL, 2.03 mmol) afforded crude pyrrolidinone **233**. Purification by flash column chromatography (Petrol:Me_2CO 4:1) gave pyrrolidinone **233** (157 mg, 80%) as a pale yellow solid; mp. 133-134 ^oC (lit. 134-136 °C); R_f 0.28 (Petrol:Me_2CO 4:1); ^1H NMR (600 MHz) δ 1.09 (3H, t, *J* = 7.5, CH_2CH_3), 1.83 (1H, ddq, *J* = 14.3, 8.2, 7.5, CH_2CH_3), 2.13 (1H, dqd, *J* = 14.3, 7.5, 4.8, CH_2CH_3), 3.32 (1H, ddd, *J* = 8.4, 6.8, 4.8, $CHCH_2$), 3.73 (3H, s, OCH_3), 4.81 (1H, dd, *J* = 6.8, 5.2, $CHNO_2$), 5.61 (1H, d, *J* = 5.3, CHPh), 6.79 (2H, app. d, *J* = 9.0, $CH_{PMPC3\text{-}H}$), 7.20-7.27 (4H, m, CH Arom.), 7.31-7.34 (3H, m, CH Arom.); HPLC (chiralcel AD 0.46 x 25 cm column, 90:10 hexane/IPA, 1 mL min-1) 35.8 min (major), 45.0 min (minor) measured 89% ee. Data in agreement to the one reported.[115]

Recrystallisation of the sample with IPA/hexane gave pyrrolidinone **233** (140 mg, 71% overall yield) as an identical pale yellow solid; $[\alpha]_D$ -62.0 (c 0.98, $CHCl_3$, 20 ^oC); HPLC measured 99% *ee*.

(3*R*, 4*R*, 5*R*)-3-Ethyl-1-(4-methoxy-phenyl)-4-nitro-5-thiophen-2-yl-pyrrolidin-2-one 241



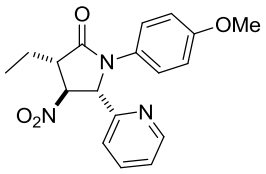
Prepared by general procedure B. Nitroacrylate **291** (76 mg, 0.580 mmol), diethyl zinc (638 µL, 0.638 mmol), imine **558** (245 mg, 1.16 mmol) and TFA (155 µL, 2.03 mmol) afforded crude pyrrolidinone **241**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone **241** (149 mg, 74%) as a pale yellow solid; mp. 91-93 ^oC (lit. 90-92 °C); R_f 0.32 (Petrol:Me_2CO 4:1); ^1H NMR (400

MHz) δ 1.12 (3H, t, J = 7.4, CH_2CH_3), 1.91 (1H, app. dquint, J = 15.0, 7.4, CH_2CH_3), 2.16 (1H, dqd, J = 14.2, 7.5, 5.2, CH_2CH_3), 3.29 (1H, ddd, J = 8.1, 6.8, 4.9, $CHCH_2$), 3.75 (3H, s, OCH_3), 4.94 (1H, dd, J = 6.4, 5.4, $CHNO_2$), 5.89 (1H, d, J = 5.1, NC*H*), 6.83 (2H, app. d, J = 8.8, $CH_{PMPC3-H}$), 6.91 (1H, dd, J = 4.0, 1.4, $CH_{thiopheneC3-H}$), 7.01 (1H, d, J = 2.8, $CH_{thiopheneC4H}$), 7.23 (2H, app. d, J = 9.2, $CH_{PMPC2-H}$), 7.27 (1H, d, J = 4.4, $CH_{thiopheneC5-H}$); $[\alpha]_D$ -48.1 (c 1, $CHCl_3$, 20 ^oC); HPLC (chiralcel AD 0.46 x 25 cm column, 90:10 hexane/IPA, 1 mL min-1) 38.8 min (major), 46.4 min (minor) measured 89% *ee*. Data in agreement to the one reported.[116]

General procedure C for the synthesis of pyrrolidin-2-ones.

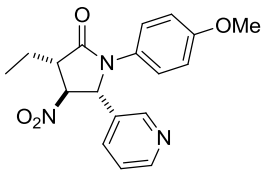
To a solution of nitroacrylate **231** (0.69 mmol) in THF (3 mL), was added $Cu(OTf)_2$ (34.0 μmol, 5 mol%). The mixture was cooled to –78 °C and dialkylzinc (0.760 mmol, of a 1.0 M solution in hexanes, 1.1 equiv.) was added fast dropwise. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. The mixture was re-cooled to -78 °C and the corresponding imine (1.38 mmol, 2.0 equiv.) in THF (2 mL) was added *via* cannula. The mixture was stirred for 20 min before TFA (2.41 mmol, 3.5 equiv.) in THF (0.5 mL) was added *via* cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt and stirred for a further 16 h. Saturated aqueous $NaHCO_3$ (20 mL) and Et_2O (20 mL) were then added and the layers separated. The aqueous phase was extracted with Et_2O (3x20 mL), and the combined organics washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to leave crude pyrrolidinone. The pyrrolidinone was then purified further by column chromatography.

(3*S, 4*S**, 5*S**)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(pyridin-2-yl)pyrrolidin-2-one 269**



Prepared by general procedure C. Nitroacrylate **231** (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine **256** (293 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone **269**. Purification by flash column chromatography (Petrol:Me_2CO 4:1) gave pyrrolidinone **269** (118 mg, 50%) as a white solid; mp. 115-117 °C; R_f 0.08 (Petrol:Me_2CO 4:1); IR υ_{max} (thin film) 3026 w (C-H), 2975 w (C-H), 1691 s (C=O), 1550 s (N=O), 1517 s, 1393 s, 1366 s (N-O), 1292 s, 1252 s, 1224 s, 1206 s, 1029 s, 755 s cm^{-1}; ^{1}H NMR (600 MHz) δ 1.11 (3H, t, *J* = 7.3, CH_2CH_3), 1.89 (1H, ddq, *J* = 14.7, 9.0, 7.4, CH_2), 2.15 (1H, dqd, *J* = 14.3, 7.6, 4.8, CH_2), 3.27 (1H, ddd, *J* = 9.0, 5.8, 4.8, $CHCH_2$), 3.73 (3H, s, OCH_3), 5.26 (1H, dd, *J* = 5.8, 4.4, $CHNO_2$), 5.64 (1H, d, *J* = 4.4, CHN), 6.78 (2H, d, *J* = 9.1, $CH_{PMPC3\text{-}H}$), 7.11 (1H, d, *J* = 7.8, $CH_{pyridine}$), 7.14 (2H, d, *J* = 9.1, $CH_{PMPC2\text{-}H}$), 7.23 (1H, ddd, *J* = 7.5, 4.5, 0.7, $CH_{pyridine}$), 7.60 (1H, td, *J* = 7.7, 1.7, $CH_{pyridine}$), 8.63 (1H, m, $CH_{pyridine}$); ^{13}C NMR (150 MHz) δ 11.3 (CH_3), 23.6 (CH_2), 49.5 ($CHCH_2$), 55.5 (OCH_3), 67.2 (CHN), 87.9 ($CHNO_2$), 114.4 (CH_{PMPC3}), 123.2 (CH_{PMPC2}), 123.9 ($CH_{pyridine}$), 126.0 ($CH_{pyridine}$), 129.4 (Cq_{PMPC1}), 137.1 ($CH_{pyridine}$), 150.7 ($CH_{pyridine}$), 155.8 ($Cq_{pyridine}$), 158.1 (Cq_{PMPC4}), 171.6 (C=O).; *m/z* (CI^+) 342 (100%, $M+H^+$); HRMS: found 342.1450, $C_{18}H_{20}N_3O_4$ requires 342.1448; Anal. Cald. For $C_{18}H_{19}N_3O_4$: C, 63.33, H, 5.61, N, 12.31. Found C, 63.04, H, 5.56, N, 12.11%.

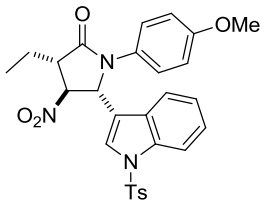
(3*S, 4*S**, 5*R**)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(pyridin-3-yl)pyrrolidin-2-one 270**



Prepared by general procedure C. Nitroacrylate **231** (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine **257** (293 mg, 1.38 mmol) and TFA (180 µL,

2.41 mmol) afforded crude pyrrolidinone **270**. Purification by flash column chromatography (Petrol:Me_2CO 4:1) gave pyrrolidinone **270** (99 mg, 42%) as a white solid; mp. 91-93 °C; R_f 0.05 (Petrol:Me_2CO 4:1); IR υ_{max} (thin film) 2963 w (C-H), 1709 (C=O), 1550 s, 1511 s, 1362 s, 1252 s, 1184 m, 1035 m, 1025 m, 832 s, 712 s cm^{-1}; ^1H NMR (600 MHz) δ 1.11 (3H, t, *J* = 7.7, CH_2CH_3), 1.88 (1H, ddq, *J* = 14.4, 8.0, 4.9, CH_2), 2.15 (1H, dqd, *J* = 14.1, 7.5, 4.8, CH_2), 3.38 (1H, ddd, *J* = 8.0, 7.3, 4.7, $CHCH_2$), 3.74 (3H, s, OCH_3), 4.80 (1H, dd, *J* = 7.2, 5.7, $CHNO_2$), 5.65 (1H, d, *J* = 5.9, CHN), 6.80 (2H, d, *J* = 9.2, $CH_{PMPC3\text{-}H}$), 7.20 (2H, d, *J* = 9.2, $CH_{PMPC2\text{-}H}$), 7.28 (1H, dt, *J* = 7.9, 1.9, $CH_{pyridine}$), 7.53 (1H, m, $CH_{pyridine}$), 8.54 (1H, d, *J* = 2.1, $CH_{pyridine}$), 8.57 (1H, dd, *J* = 4.8, 1.4, $CH_{pyridine}$); ^{13}C NMR (150 MHz) δ 10.7 (CH_3), 23.2 (CH_2), 48.8 ($CHCH_2$), 55.5 (OCH_3), 63.6 (NCH), 89.9 ($CHNO_2$), 114.6 (CH_{PMPC3}), 124.2 (CH_{PMPC4}), 125.3 ($CH_{pyridine}$), 128.7 (Cq_{PMPC1}), 133.0 ($Cq_{pyridine}$), 134.4 ($CH_{pyridine}$), 148.8 ($CH_{pyridine}$), 150.8 ($CH_{pyridine}$), 158.0 (Cq_{PMPC4}), 170.7 (C=O); *m/z* (CI^+) 342 (100%, $M+H^+$), 295 (10%); HRMS: found 342.1461, $C_{18}H_{20}N_3O_4$ requires 342.1458; Anal. Cald. For $C_{18}H_{19}N_3O_4$: C, 63.33, H, 5.61, N, 12.31. Found C, 63.36, H, 5.62, N, 12.24%.

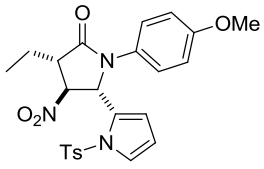
(3*S, 4*S**, 5*R**)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(1-tosyl-1*H*-indol-3-yl)pyrrolidin-2-one 271**



Prepared by general procedure C. Nitroacrylate **231** (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine **260** (558 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone **271**. Purification by flash column chromatography (Petrol:Me_2CO 4:1) gave pyrrolidinone **271** (206 mg, 56%) as a yellow solid; mp. 131-132 °C; R_f 0.08 (Petrol:Me_2CO 4:1); IR υ_{max} (thin film) 3104 w (C-H), 2935 w (C-H), 1709 s (C=O), 1553 s (N=O), 1511 s, 1445 s, 1362 s (N-O), 1350 s, 1244 s, 1189 m, 1174 s, 1135 m, 1123 m, 1094 m, 1027 m, 977 m, 828 s, 816 m, 746 s, 706 m, 678 s cm^{-1}; ^1H NMR (600 MHz) δ 1.08 (3H, t, *J* = 7.4, CH_2CH_3), 1.82 (1H, ddq, *J* = 14.2, 8.5, 7.2, CH_2CH_3), 2.15 (1H, dqd, *J* = 14.2, 7.6, 4.8,

CH_2CH$_3$), 2.43 (3H, s, ArCH_3), 3.38 (1H, ddd, *J* = 8.5, 6.7, 4.8, C*H*CH$_2$), 3.76 (3H, s, OCH_3), 4.97 (1H, dd, *J* = 6.7, 5.2, C*H*NO$_2$), 5.83 (1H, d, *J* = 5.3, NC*H*), 6.76 (2H, d, *J* = 9.0, C$H_{PMPC3-H}$), 7.13 (2H, d, *J* = 8.4, C$H_{tosylC3-H}$), 7.25 (2H, d, *J* = 9.0, C$H_{PMPC4-H}$), 7.29 (1H, m, CH_{indole}), 7.35 (1H, m, CH_{indole}), 7.46 (4H, m, C*H* Arom.), 7.93 (1H, d, *J* = 8.4, C$H_{indoleC6-H}$); ^{13}C NMR (150 MHz) δ 11.1 (CH$_2$*C*H$_3$), 21.7 (Ar*C*H$_3$), 23.6 (*C*H$_2$), 49.2 (*C*HCH$_2$), 55.5 (O*C*H$_3$), 59.5 (N*C*H), 88.2 (*C*HNO$_2$), 114.3 (*C*H$_{PMPC3}$), 114.4 (*C*H$_{indoleC6}$), 118.3 (*C*q$_{indoleC3}$), 119.2 (*C*H$_{indoleC2}$), 124.2 (*C*H$_{indole}$), 124.8 (*C*H$_{PMPC2}$), 125.8 (*C*H$_{indole}$), 126.1 (*C*H$_{indole}$), 126.8 (*C*H$_{tosylC2}$), 127.5 (*C*q$_{indoleC4}$), 129.3 (*C*q$_{PMPC1}$), 130.0 (*C*H$_{tosylC3}$), 134.5 (*C*q $_{indoleC9}$), 135.7 (*C*q$_{tosylC1}$), 145.4 (*C*q$_{tosylC2}$), 157.8 (*C*q$_{PMPC4}$), 170.7 (*C*=O); *m/z* (ESI$^+$) 534 (100%, M+H$^+$), 445 (40%), 535 (30%); HRMS: found 534.1674, $C_{28}H_{27}N_3O_6S$ requires 534.1699; Anal. Cald. For $C_{28}H_{26}N_3O_6S$: C, 63.03, H, 5.10, N, 7.87. Found C, 63.18, H, 5.48, N, 7.40%.

(3*S, 4*S**, 5*S**)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(1-tosyl-1*H*-pyrrol-2-yl)pyrrolidin-2-one 272**

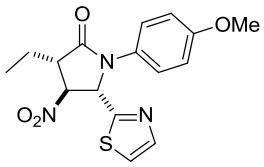


Prepared by general procedure C. Nitroacrylate **231** (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine **263** (489 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone **272**. Purification by flash column chromatography (Petrol:Me$_2$CO 4:1) gave pyrrolidinone **272** as an inseparable 85:15 mixture of diastereoisomers (110 mg, 33%), as a yellow solid; mp. 147-148 °C; R$_f$ 0.18 (Petrol:Me$_2$CO 4:1); diastereoisomer ratio calculated by C*H*Et signal, δ major = 2.86, δ minor = 3.01; IR υ$_{max}$ (thin film) 3004 w (C-H), 2994 w (C-H), 1699 s (C=O), 1549 s (N=O), 1512 s, 1368 s (N-O), 1247 s, 1234 m, 1190 m, 1181 m, 1171 s, 1153 s, 1130 m, 1088 m, 1055 m, 1039 m, 832 s, 815 s, 736 s, 703 s, 671 s cm^{-1}; ^{1}H NMR (600 MHz, 60 ^{o}C) δ 1.13 (3H, t, *J* = 7.4, CH$_2$CH_3), 1.59 (1H, m, CH_2CH$_3$), 2.12 (1H, dqd, *J* = 14.8, 7.4, 4.8, CH_2CH$_3$), 2.50 (3H, s, ArCH_3), 2.86 (1H, ddd, *J* = 10.3, 4.7, 2.3, C*H*CH$_2$), 3.74 (3H, s, OCH_3), 4.94 (1H, t, *J* = 2,4, 1.6, C*H*NO$_2$), 6.02 (1H, s, NC*H*), 6.10 (1H, s, C$H_{pyrroleC3-H}$), 6.22 (1H, t, *J* = 3.4, C$H_{pyrroleC4-H}$), 6.58 (2H, d, *J* = 9.1, C$H_{PMPC3-H}$), 6.91 (2H, d, *J* = 9.2, C$H_{PMPC2-H}$), 7.38 (3H, m, C$H_{tosylC3-H}$ and

C*H*$_{pyrroleC5-H}$), 7.63 (2H, d, *J* = 8.2, C*H*$_{tosylC2-H}$); ^{13}C NMR (150 MHz) δ 12.0 (CH_2CH_3), 21.7 (Ar*C*H$_3$), 25.5 (*C*H$_2$), 52.3 (*C*HCH$_2$), 55.3 (O*C*H$_3$), 59.4 (N*C*H), 86.4 (*C*HNO$_2$), 111.7 (*C*H$_{pyrroleC3}$), 113.9 (*C*H$_{PMPC3}$), 114.9 (*C*H$_{pyrroleC4}$), 123.2 (*C*H$_{PMPC2}$), 124.0 (*C*H$_{pyrroleC5}$), 126.9 (*C*H$_{tosylC2}$), 128.3 (*C*q$_{pyrroleC2}$), 129.8 (*C*H$_{tosylC3}$), 130.5 (*C*q$_{PMPC1}$), 135.3 (*C*q$_{tosylC1}$), 145.9 (*C*q$_{tosylC4}$), 157.1 (*C*q$_{PMPC4}$), 171.6 (*C*=O); *m/z* (EI$^+$) 483 (20%, M$^+$), 281 (24%), 155 (22%, Ts$^+$), 91 (100%, PhCH$_2^+$); HRMS: found 483.1451, $C_{24}H_{25}N_3O_6S$ requires 483.1464; Anal. Cald. For $C_{24}H_{25}N_3O_6S$: C, 55.32, H, 4.93, N, 12.10. Found C, 55.23, H, 4.89, N, 12.02%.

Minor diastereomer: ^{1}H NMR (600 MHz, 60 ^{o}C) δ 1.12 (3H, t, *J* = 7.4, CH_2CH_3), 1.33 (1H, m, C*H*$_2$CH$_3$), 2.12 (1H, m, C*H*$_2$CH$_3$), 2.47 (3H, s, ArC*H*$_3$), 3.01 (1H, ddd, *J* = 9.6, 7.3, 4.6, C*H*CH$_2$), 3.74 (3H, s, OC*H*$_3$), 5.33 (1H, d, *J* = 7.4, C*H*NO$_2$), 5.73 (1H, s, NC*H*), 6.20 (1H, s, C*H*$_{pyrroleC3-H}$), 6.27 (1H, t, *J* = 3.5, C*H*$_{pyrroleC4-H}$), 6.61 (2H, d, *J* = 9.1, C*H*$_{PMPC3-H}$), 6.98 (2H, d, *J* = 9.0, C*H*$_{PMPC2-H}$), 7.32 (3H, m, C*H*$_{tosylC3-H}$ and C*H*$_{pyrroleC5-H}$), 7.60 (2H, d, *J* = 8.2, C*H*$_{tosylC2-H}$); ^{13}C NMR (150 MHz) δ 12.2 (CH_2CH_3), 18.9 (*C*H$_2$), 21.7 (Ar*C*H$_3$), 45.8 (*C*HCH$_2$), 55.3 (O*C*H$_3$), 60.0 (N*C*H), 86.6 (*C*HNO$_2$), 112.0 (*C*H$_{pyrroleC3}$), 113.9 (*C*H$_{PMPC3}$), 114.6 (*C*H $_{pyrroleC4}$), 123.2 (*C*H$_{PMPC2}$), 124.4 (*C*H$_{pyrroleC5}$), 126.7 (*C*H$_{tosylC2}$), 129.6 (*C*H$_{tosylC3}$), 171.0 (*C*=O), 4 carbons missing.

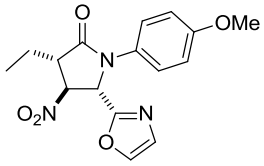
(3*S, 4*S**, 5*S**)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(thiazol-2-yl)pyrrolidin-2-one 273**



Prepared by general procedure C. Nitroacrylate **231** (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine **264** (301 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone **273**. Purification by flash column chromatography (Petrol:EtOAc 7:3) gave pyrrolidinone **273** (139 mg, 58%) as a yellow solid; mp. 121-122 °C; R_f 0.31 (Petrol:EtOAc 7:3); IR υ_{max} (thin film) 2961 w (C-H), 1716 s (C=O), 1558 s (N=O), 1512 s, 1440 m, 1390 m, 1363 m (N-O), 1247 s, 1187 m, 1029 s, 832 s, 782 s, 752 s cm^{-1}; ^{1}H NMR (600 MHz) δ 1.14 (3H, t, *J* = 7.1,

CH_2CH_3), 1.90 (1H, ddq, *J* = 14.3, 8.9, 7.1, CH_2CH_3), 2.15 (1H, dqd, *J* = 14.0, 7.6, 4.9, CH_2CH_3), 3.25 (1H, dt, *J* = 9.0, 5.0, $CHCH_2$), 3.78 (3H, s, OCH_3), 5.36 (1H, dd, *J* = 5.1, 3.8, $CHNO_2$), 6.02 (1H, d, *J* = 4.2, NC*H*), 6.87 (2H, d, *J* = 9.2, $CH_{PMPC3-H}$), 7.25 (2H, d, *J* = 9.2, $CH_{PMPC2-H}$), 7.31 (1H, d, *J* = 3.0, $CH_{thiazoleC5-H}$), 7.80 (2H, d, *J* = 3.4, $CH_{thiazoleC4-H}$); ^{13}C NMR (150 MHz) δ 11.2 (CH_3), 23.7 (CH_2), 49.7 ($CHCH_2$), 55.5 (OCH_3), 63.3 (NCH), 87.4 ($CHNO_2$), 114.6 (CH_{PMPC3}), 121.0 ($CH_{thiazoleC5}$), 126.4 (CH_{PMPC2}), 128.7 (Cq_{PMPC1}), 143.6 ($CH_{thiazoleC5}$), 158.6 (Cq_{PMPC4}), 165.7 ($Cq_{thiazoleC2}$), 171.1 (*C*=O).; *m/z* (EI^+) 347 (100%, M^+), 300 (55%, M^+- HNO_2); HRMS: found 347.0940, $C_{16}H_{17}N_3O_4S$ requires 347.0934; Anal. Cald. For $C_{16}H_{17}N_3O_4S$: C, 59.61, H, 5.21, N, 8.69. Found C, 59.52, H, 5.20, N, 8.61%.

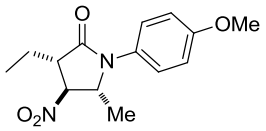
(3*S, 4*S**, 5*S**)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(oxazol-2-yl)pyrrolidin-2-one 274**



Prepared by general procedure C. Nitroacrylate **231** (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine **265** (279 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone **274**. Purification by flash column chromatography (Petrol:Me_2CO 4:1) gave pyrrolidinone **274** (121 mg, 53%) as a white solid; mp. 97-98 °C; R_f 0.15 (Petrol:Me_2CO 4:1); IR υ_{max} (thin film) 2964 w (C-H), 1706 s (C=O), 1562 s (N=O), 1509 s, 1387 m (N-O), 1243 s, 1179 m, 1115 m, 1031 m, 834 s, 779 s cm^{-1}; ^{1}H NMR (600 MHz) δ 1.17 (3H, t, *J* = 7.5, CH_2CH_3), 1.96 (1H, ddq, *J* = 14.3, 8.7, 7.4, CH_2CH_3), 2.19 (1H, dqd, *J* = 14.3, 7.6, 4.9, CH_2CH_3), 3.25 (1H, ddd, *J* = 8.7, 5.7, 4.9, $CHCH_2$), 3.78 (3H, s, OCH_3), 5.28 (1H, dd, *J* = 5.6, 4.4, $CHNO_2$), 5.79 (1H, d, *J* = 4.4, NC*H*), 6.86 (2H, d, *J* = 9.0, $CH_{PMPC3-H}$), 7.11 (1H, s, $CH_{oxazoleC4-H}$), 7.19 (2H, d, *J* = 9.0, $CH_{PMPC2-H}$), 7.62 (1H, s, $CH_{oxazoleC5-H}$); ^{13}C NMR (150 MHz) δ 11.1 (CH_3), 23.4 (CH_2), 49.2 ($CHCH_2$), 55.5 (OCH_3), 59.6 (NCH), 85.6 ($CHNO_2$), 114.6 (CH_{PMPC3}), 126.4 (CH_{PMPC2}), 128.2 ($CH_{oxazoleC4}$), 128.6 (Cq_{PMPC1}), 140.5 ($CH_{oxazoleC4}$), 158.8 (Cq_{PMPC4}), 159.3 ($Cq_{oxazoleC2}$), 170.8 (*C*=O); *m/z* (EI^+) 331 (100%, M^+), 284 (72%, M^+-HNO_2); HRMS: found 331.1155, $C_{16}H_{17}N_3O_5$

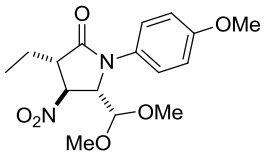
requires 331.1163; Anal. Cald. For $C_{16}H_{17}N_3O_5$: C, 58.00, H, 5.17, N, 12.68. Found C, 57.97, H, 5.09, N, 12.64%.

(3*S, 4*S**, 5*R**)-3-ethyl-1-(4-methoxyphenyl)-5-methyl-4-nitropyrrolidin-2-one 275**



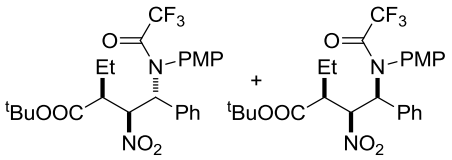
Prepared by general procedure C, with the exception that imine **266** was formed and used *in situ*. To a solution of acetaldehyde (77 μL, 1.38 mmol) in THF (5 mL) were added under Nitrogen dried 4Å molecular sieves (1.40 g) and the mixture cooled at -78 ^{o}C. A solution of *para*-anisidine (170 mg, 1.38 mmol) in THF (1 mL) was then added and the mixture stirred at this temperature for 1.5 h. The solution was then transferred into the reaction *via* cannula. Nitroacrylate **231** (100 mg, 0.69 mmol) diethylzinc (760 μL, 0.760 mmol), freshly prepared cold (-78 ^{o}C) solution of imine **266** (1.38 mmol) and TFA (180 μL, 2.41 mmol) afforded crude pyrrolidinone **275**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone **275** (78 mg, 40%) as a colourless oil; R_f 0.22 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2967 w (C-H), 1702 s (C=O), 1554 s (N=O), 1513 s, 1368 m (N-O), 1248 s, 1033 m, 834 m cm^{-1}; ^{1}H NMR (600 MHz) δ 1.07 (3H, t, *J* = 7.4, CH_2CH_3), 1.35 (3H, d, *J* = 6.3, $CHCH_3$), 1.79 (1H, m, CH_2CH_3), 2.08 (1H, m, OCH_2CH_3), 3.26 (1H, ddd, *J* = 8.3, 7.3, 4.7, $CHCH_2$), 3.81 (3H, s, OCH_3), 4.49 (1H, app q, *J* = 6.2, $NCHCH_3$), 4.60 (1H, dd, *J* = 7.2, 5.7, $CHNO_2$), 6.93 (2H, app d, *J* = 8.9, $CH_{PMPC3\text{-}H}$), 7.18 (2H, app d, *J* = 8.9, $CH_{PMPC2\text{-}H}$); ^{13}C NMR (125 MHz) δ 10.6 (CH_2CH_3), 19.3 ($CHCH_3$), 23.1 (CH_2CH_3),48.5 ($CHCH_2$), 55.4 (OCH_3), 58.0 ($CHCH_3$), 89.3 ($CHNO_2$), 114.5 (CH_{PMPC3}), 126.6 (CH_{PMPC2}), 128.4 (Cq_{PMPC1}), 158.4 (Cq_{PMPC4}), 170.4 (C=O); *m/z* (EI^{+}) 278 (5%, M^{+}), 231 (21%), 148 (13%), 134 (24), 91 (100%); HRMS found 278.12631, $C_{14}H_{18}N_2O_4$ requires 278.12611; Anal. Cald. for $C_{14}H_{18}N_2O_4$: C, 60.42, H, 6.52, N, 10.07. Found C, 60.31, H, 6.61, N, 9.77%.

(2*S, 3*S**, 4*S**)- 3-ethyl-5-(dimethoxymethyl)-1-(4-methoxyphenyl)-4-nitropyrrolidin-2-one 276**



Prepared by general procedure C. Nitroacrylate **231** (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), imine **267** (288 mg, 1.38 mmol) and TFA (180 µL, 2.41 mmol) afforded crude pyrrolidinone **276**. Purification by flash column chromatography (Petrol:EtOAc 7:3) gave pyrrolidinone **276** (147 mg, 63%) as a white solid; mp. 112-113 °C; R_f 0.41 (Petrol:EtOAc 7:3); IR υ_{max} (thin film) 2939 w (C-H), 1698 s, 1548 s (N=O), 1510 s, 1370 m (N-O), 1249 s, 1069 m, 1034 m, 834 m, 754 m cm^{-1}; ^{1}H NMR (600 MHz) δ 1.14 (3H, t, *J* = 7.4, CH_2CH_3), 1.81 (1H, ddq, *J* = 14.0, 9.7, 7.2, CH_2CH_3), 2.09 (1H, dqd, *J* = 14.0, 7.4, 4.3, CH_2CH_3), 2.97 (1H, dt, *J* = 9.8, 4.6, $CHCH_2$), 3.38 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 3.84 (3H, s, $ArOCH_3$), 4.24 (1H, d, *J* = 2.4, $CH(OCH_3)_2$), 4.76 (1H, dd, *J* = 3.2, 2.6, NCH), 5.07 (1H, dd, *J* = 4.9, 3.4, $CHNO_2$), 6.97 (2H, d, *J* = 8.9, $CH_{PMPC3-H}$), 7.30 (2H, d, *J* = 9.0, $CH_{PMPC2-H}$); ^{13}C NMR (150 MHz) δ 11.3 (CH_2CH_3), 23.1 (CH_2), 50.2 ($CHCH_2$), 55.5 (OCH_3), 56.9 (OCH_3), 57.9 (OCH_3), 64.3 (CHN), 82.1 ($CHNO_2$), 102.3 ($CH(OMe)_2$), 114.7 (CH_{PMPC3}), 126.2 (CH_{PMPC2}), 128.8 (Cq_{PMPC1}), 158.3 (Cq_{PMPC4}), 171.7 (C=O); *m/z* (EI^+) 338 (75%, M^+), 217 (85%, M^+-NO_2 -$CH(OMe)_2$), 114 (100%); HRMS found 338.1472, $C_{16}H_{22}N_2O_6$ requires 359.1219; Anal. Cald. for $C_{16}H_{22}N_2O_6$: C, 56.80, H, 6.55, N, 8.28. Found C, 56.70, H, 6.51, N, 8.11%.

(2*S,3*S**,4*R**)-*tert*-butyl 4-(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)-2-ethyl-3-nitro-4-phenylbutanoate 299**



syn, anti-**299** *syn, syn*-**299**

dr 65:35

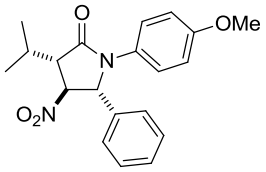
To a solution of nitroacrylate **296** (222 mg, 1.28 mmol) in THF (5 mL), was added $Cu(OTf)_2$ (5 mol%, 23 mg) and the mixture cooled to -78 °C. A solution of Et_2Zn

(1.32 mL, of a 1 M solution in hexanes, 1.32 mmol) was then added dropwise. The orange mixture was stirred at this temperature for 10 min and then at rt for 1.5 h. The mixture was then recooled to -78 °C and imine **281** (540 mg, 2.56 mmol) in THF (3 mL) was added *via* cannula. The mixture was stirred for 10 min before TFA (340 µL, 4.48 mmol) in THF (2 mL) was added dropwise. The mixture was stirred at this temperature for a further 1 h, then warmed to rt and stirred for a further 1 h. The mixture was then cooled to 0 °C and pyridine (0.51 mL, 6.4 mmol) followed by trifluoroacetic anhydride (0.89 mL, 6.4 mmol) were added. The mixture was then warmed to rt and stirred for a further 2 h. The mixture was then washed with 2 M aqueous HCl (3x10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave crude trifluoroacetamides **299**. Purification by flash column chromatography (Petrol:DCM 4:6) gave trifluoroacetamides **299** (170 mg, 26%) as a colourless oil which was found to be a mixture of two diastereomers 65:35; diastereomer ratio calculated by C*H*Et signal, δ major = 2.91, δ minor = 2.80; R_f 0.58 (Petrol:DCM 4:6); Major diastereomer: IR υ_{max} (thin film) 2976 w (C-H), 1727 m (C=O), 1698 s, 1558 m (N=O), 1510 m, 1206 s, 1034 m, 840 m, 734 m, 699 m cm^{-1}; ^{1}H NMR (600 MHz) δ 1.09 (3H, t, *J* = 7.4, OC*H*$_3$), 1.49 (9H, s, C(C*H*$_3$)$_3$), 1.76 (1H, dqd, *J* = 12.7, 7.5, 5.3, C*H*$_2$CH$_3$), 1.98 (1H, m, C*H*$_2$CH$_3$), 2.91 (1H, ddd, *J* = 9.4, 5.2, 4.1, C*H*Et), 3.81 (3H, s, OC*H*$_3$), 5.71 (1H, d, *J* = 10.2, C*H*Ph), 5.86 (1H, dd, *J* = 10.2, 3.9, C*H*NO$_2$), 6.50-7.43 (7H, m, Arom. C*H*); ^{13}C NMR (150 MHz) δ 11.7 (CH$_2$*C*H$_3$), 23.3 (*C*H$_2$), 27.8 (C(*C*H$_3$)$_3$), 48.3 (*C*HEt), 55.4 (O*C*H$_3$), 65.1 (*C*HPh), 82.7 and 82.7 (*C*(CH$_3$)$_3$), 87.6 (*C*HNO$_2$), 113.4, 114.3, 128.7, 128.8, 129.4, 129.5, 130.6, 131.9, 133.1, 133.1, 133.8 (*C*H Arom.), 158.1 (q, *J* = 35.7, *C*F$_3$), 160.3 (*C*=OCF$_3$), 169.2 (O*C*=O); ^{19}F NMR (282 MHz) δ -67.85 (3F, s, C*F*$_3$); *m/z* (CI$^+$) 511 (M +1, 20%), 545 (100%, M +H-^{t}Bu), 408 (43%, M –^{t}Bu-CO$_2$); HRMS: found 511.20545, $C_{25}H_{29}F_3N_2O_6$ requires 511.20560; Anal. Cald. For $C_{25}H_{30}F_3N_2O_6$: C, 58.82, H, 5.73, N, 5.49. Found C, 59.08, H, 6.06, N, 5.24%.

Minor diastereoisomer: ^{1}H NMR (600 MHz) δ 1.05 (3H, t, *J* = 7.4), 1.58 (9H, s, C(C*H*$_3$)$_3$), 1.63 (1H, dqd, *J* = 11.4, 7.1, 6.6, C*H*$_2$CH$_3$), 2.05 (1H, m, C*H*$_2$CH$_3$), 2.80 (1H, dt, *J* = 11.4, 2.2, C*H*Et), 3.81 (3H, s, OC*H*$_3$), 5.52 (1H, dd, *J* = 11.6, 2.2, C*H*NO$_2$), 5.97 (1H, d, *J* = 8.7, C*H*Ph), 6.50-7.43 (7H, m, Arom. C*H*); ^{13}C NMR (150 MHz) δ 12.8 (CH$_2$*C*H$_3$), 18.9 (*C*H$_2$), 28.0 (C(*C*H$_3$)$_3$), 48.4 (*C*HEt), 55.4 (O*C*H$_3$), 58.7 (*C*HPh), 82.7 and 82.7 (*C*(CH$_3$)$_3$), 86.8 (*C*HNO$_2$), 113.6, 113.9 (*C*H Arom.), 158.2 (q,

J = 35.7, CF$_3$), 160.1 (C=OCF$_3$), 170.0 (OC=O), the rest of the ^{13}C peaks could not be distinguished between the two diastereomers; ^{19}F NMR (282 MHz) δ -67.36 (3F, s, CF_3).

(3*S, 4*S**, 5*R**)-3-isopropyl-1-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one 282**

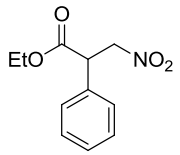


Prepared by general procedure C. Nitroacrylate **231** (100 mg, 0.690 mmol), diisopropylzinc (0.760 mmol, of a 0.356 M solution in hexane, 1.1 equiv.), imine **281** (291 mg, 1.38 mmol) and TFA (180 μL, 2.41 mmol) afforded crude pyrrolidinone **282**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave **282** (125 mg, 51%) as a white solid; mp. 140-141 °C; R_f 0.50 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2961.6 w (C-H), 1707.7 m (C=O), 1556.8 m (N=O), 1513 s, 1369 w (N-O), 1249 m, 1032 w, 700 w cm^{-1}; ^{1}H NMR (600 MHz) δ 1.07 (6H, dd, J = 8.3, 7.0, CH_3), 2.55 (1H, m, CH(CH$_3$)$_2$), 3.43 (1H, dd, J = 7.6, 4.5, CHC=O), 3.73 (3H, s, OCH_3), 4.88 (1H, dd, J = 7.6, 5.9, CHNO$_2$), 5.52 (1H, d, J = 5.9, NCHPh), 6.79 (2H, app d, J = 9.1, C$H_{PMPC3-H}$), 7.19 (2H, m, CH Arom.), 7.23 (2H, app d, J = 9.1, C$H_{PMPC2-H}$), 7.28-7.35 (3H, m, CH Arom.); ^{13}C NMR (150 MHz) δ 18.3 and 19.6 (CH$_3$), 28.0 (CH(CH$_3$)$_2$), 53.3 (CHC=O), 55.3 (OCH$_3$), 65.9 (NCHPh), 88.4 (CHNO$_2$), 114.1 (CH$_{PMPC3}$), 125.0 (CH Arom.), 126.6 (CH Arom.), 129.1 (CH Arom.), 129.2 (Cq Arom.), 129.3 (CH Arom.), 137.2 (Cq Arom.), 157.5 (Cq$_{PMPC4}$), 170.5 (C=O); *m/z* (ESI$^+$) 355 (M+H$^+$, 20%), 308 (M$^+$-NO$_2$, 100%), 266 (M+H $^+$-NO$_2$-C$_3$H$_7$, 30%); HRMS: found 355.1647, $C_{20}H_{23}N_2O_4$ requires 355.1658; Anal. Cald. For $C_{20}H_{22}N_2O_4$: C, 67.78, H, 6.26, N, 7.90. Found C, 67.70, H, 6.22, N, 7.84%.

Also prepared from the reaction of nitroalkene **370** with Superhydride®. To a solution of nitroalkene **370** (187 mg, 1.00 mmol) in THF (10 mL) was added Superhydride® (1.05 mL, 1 M in THF, 1.05 mmol) and the suspension stirred at rt for 30 min. The mixture was then cooled to -78 °C and a solution of imine **281** (2.0 mmol) in THF (6 mL) was added, followed in 10 min by TFA (3.0 mmol) in THF (1 mL) dropwise.

The mixture was stirred at this temperature for 1 h and then warmed to rt and stirred for a further 24 h. Saturated aqueous $NaHCO_3$ (10 mL) was then added and the mixture extracted with Et_2O (3x10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude pyrrolidinone **282**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave **282** (138 mg, 39%) as a white solid, same as the one reported above.

Ethyl 3-nitro-2-phenylpropanoate 279

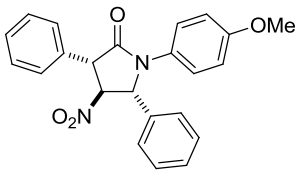


To a solution of nitroacrylate **231** (100 mg, 0.690 mmol) in THF (3 mL), was added $Cu(OTf)_2$ (12 mg, 34 μmol, 5 mol%). The mixture was cooled to –78 °C and the diphenylzinc solution (0.760 mmol, 1.1 equiv.) was added fast dropwise. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. Saturated aqueous NH_4Cl (20 mL) and Et_2O (20 mL) was then added and the layers separated. The aqueous phase was extracted with Et_2O (3x20 mL), and the combined organics washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave crude nitroalkane **279**. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave **279** (92 mg, 60%) as a colourless oil; R_f 0.35 (Petrol:Et_2O 9:1); ^{1}H NMR (600 MHz) δ 1.24 (3H, t, *J* = 7.4, CH_2CH_3), 4.17 (1H, m, OCH_2CH_3), 4.26 (1H, m, OCH_2CH_3), 4.44 (1H, dd, *J* = 10.0, 5.1, C*H*Ph), 3.73 (3H, s, OCH_3), 4.56 (2H, dd, *J* = 14.7, 5.2, CH_2NO_2), 5.12 (1H, dd, *J* = 14.6, 10.0, CH_2NO_2), 7.30-7.38 (5H, m, C*H* Arom.). Data in agreement to the one reported.[175]

Also prepared using a cuprate reagent according to the reported procedure.[253] To a mixture of $CuBr{\cdot}SMe_2$ (205 mg, 1.00 mmol) in THF (2.5 mL) was added at -40 °C, PhMgBr (330 μL, 3 M in Et_2O, 1.00 mmol) and the mixture stirred for 30 min, then cooled to -78 °C and a solution of nitroalkene **231** (145 mg, 1.00 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for 30 min, then warmed to rt and stirred until complete consumption of the nitroalkene (TLC, 3 h). Saturated aqueous NH_4Cl (20 mL) was then added and the mixture extracted with Et_2O (3x10 mL). The

combined organics were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), died over $MgSO_4$ and evaporated *in vacuo* to give crude nitroalkane **279**. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave **279** (108 mg, 48%) as a colourless oil same as the one reported above.

(3*S, 4*S**, 5*R**)-1-(4-methoxyphenyl)-4-nitro-3,5-diphenylpyrrolidin-2-one 278**

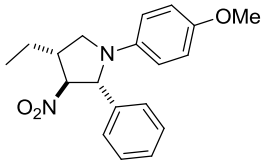


A solution of nitroalkane **279** (121 mg, 0.540 mmol) in THF (3 mL), was cooled to -78 °C and a solution of ^{n}BuLi (320 µL, 0.540 mmol, 1.0 equiv., 1.7 M solution in hexanes) was added dropwise. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 30 min. The mixture was re-cooled to -78 °C and the PMP-protected imine (228 mg, 1.08 mmol, 2.0 equiv.) in THF (2 mL) was added *via* cannula. The mixture was stirred for 20 min before TFA (104 µL, 1.35 mmol, 2.5 equiv.) in THF (0.5 mL) was added *via* cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt for 16 h. Saturated aqueous $NaHCO_3$ (20 mL) and Et_2O (20 mL) were then added and the layers separated. The aqueous phase was extracted with Et_2O (3x20 mL) and the combined organics were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave crude pyrrolidinone **278**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave **278** (106 mg, 51%) as a white solid; mp. 136-137 °C; R_f 0.24 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 1721 m (C=O), 1553 s (N=O), 1510 m, 1247 m, 1177 m, 1036 m, 847 m, 753 m, 714 s, 696 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.73 (3H, s, OC*H*$_3$), 4.69 (1H, d, *J* = 8.0, C*H*C=O), 5.15 (1H, dd, *J* = 8.0, 6.3, $CHNO_2$), 5.68 (1H, d, *J* = 6.2, NC*H*), 6.81 (2H, app d, *J* = 6.2, C*H* Arom.), 7.23-7.45 (12H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 53.3 (*C*HC=O), 55.3 (O*C*H$_3$), 65.5 (N*C*H), 93.0 (*C*HNO_2), 114.2 (*C*H$_{PMPC3}$), 125.2 (*C*H Arom.), 126.9 (*C*H Arom.), 128.2 (*C*H Arom.), 128.5 (*C*H Arom.), 129.1 (Cq Arom.), 129.3 (*C*H Arom.), 129.3 (Cq Arom.) 129.4 (*C*H$_{PMPC2}$), 134.9 (Cq$_{PMPC1}$), 157.7 (Cq$_{PMPC4}$), 169.1 (*C*=O).; *m/z* (CI^+) 389 ($M+H^+$, 6%), 342 (100%, M - NO_2); HRMS: found 389.15036, $C_{23}H_{21}N_2O_4$

requires 389.15013; Anal. Cald. For $C_{23}H_{20}N_2O_4$: C, 71.12, H, 5.19, N, 7.21. Found C, 70.91, H, 5.17, N, 7.15%.

3.4.1.3 Further functionalisation of pyrrolidinones

(2*R, 3*S**, 4*R**)-4-Ethyl-1-(4-methoxy-phenyl)-3-nitro-2-phenyl-pyrrolidine 247**



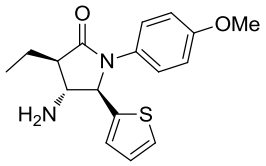
Prepared by a modification of the reported procedure.[119] To a solution of pyrrolidinone **233** (350 mg, 1.03 mmol) in THF (25 mL) at 0 °C was added $BH_3 \cdot THF$ complex (3.61 mL, of a 1.0 M solution in THF, 3.61 mmol, 3.5 equiv.) dropwise. The mixture was stirred at 0 °C until no more effervescence was observed and then heated to reflux until the starting pyrrolidinone was consumed (TLC, 4.5 h). The mixture was cooled to rt and MeOH (50 mL) was added before being concentrated *in vacuo* to give crude pyrrolidine **247**. Purification by flash column chromatography (Petrol:Me_2CO 4:1) gave pyrrolidine **247** (316 mg, 94%, lit. 79%) as a yellow solid; mp. 47-48 °C (50-52 °C); R_f 0.21 (Petrol:Me_2CO 4:1); ^{1}H NMR (600 MHz) δ 0.97 (3H, t, *J* = 7.3, C*H*$_3$), 1.58 (2H, m, C*H*$_2$CH$_3$), 2.85 (1H, m, C*H*Et), 3.67 (1H, dd, *J* = 9.1, 5.5, NC*H*$_2$), 3.72 (3H, s, OCH$_3$), 3.85 (1H, dd, *J* = 9.1, 8.1, NC*H*$_2$), 4.76 (1H, app. t, *J* = 5.2, C*H*NO$_2$), 5.13 (1H, d, *J* = 4.7, C*H*Ph), 6.46-6.50 (2H, m, C*H* Arom.), 6.74-6.78 (2H, m, C*H* Arom.), 7.28-7.34 (5H, m, C*H* Arom.). Data in agreement to the one reported.[116]

General procedure D for the reduction of the nitro group

To a solution of pyrrolidinone (0.29 mmol) in EtOAc/MeOH (2:1, 6 mL) at 0 °C, was added HCl (1.47 mL of an aqueous 6 M sol, 8.82 mmol, 30.0 equiv.). Zinc dust (1.15 g, 17.6 mmol, 60.0 equiv.) was added portionwise over 20 min. The mixture was then warmed to rt and stirred for a further 15 hr. Saturated aqueous $NaHCO_3$ (30 mL) was added carefully, followed by EtOAc (20 mL). The layers were separated and the aqueous layer extracted with EtOAc (2x20 mL), and the combined organics washed

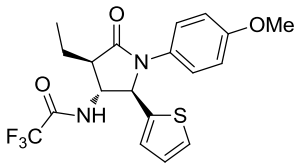
with saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The pH of the aqueous layer was tested and additional saturated aqueous $NaHCO_3$ was added as necessary to reach pH 9. The organics were dried over $MgSO_4$ and concentrated *in vacuo* to give the product diamine.

(3*R*, 4*R*, 5*R*)-4-amino-3-ethyl-1-(4-methoxyphenyl)-5-(thiophen-2-yl)pyrrolidin-2-one 561



Produced by general procedure D. Pyrrolidinone **241** (138 mg, 0.400 mmol, 89% *ee*), HCl (2.00 mL, 12.0 mmol, 30.0 equiv.) and zinc dust (1.57 g, 24.0 mmol, 60.0 equiv.) afforded crude amine **561**. Purification by flash column chromatography (Petrol:Me_2CO 7:3) gave amine **561** as a yellow oil (113 mg, 89%); R_f 0.25 (Petrol:Me_2CO 7:3); $[\alpha]_D$ -22.2 (c 1, $CHCl_3$, 20 ^oC); IR υ_{max} (thin film) 3363 br (N-H), 2962 w (C-H), 1687 s (C=O), 1509 s, 1367 m, 1295 m, 1244 s, 1029 m, 830 m, 699 m cm^{-1}; ^1H NMR (600 MHz) δ 1.11 (3H, t, *J* = 7.5, CH_3), 1.82 (1H, m, CH_2), 1.96 (1H, dqd, *J* = 14.1, 7.6, 5.2, CH_2), 2.17 (2H, br, NH_2), 2.38 (1H, ddd, *J* = 9.4, 6.7, 5.1, C*H*Et), 3.32 (1H, dd, *J* = 9.3, 7.2, C*H*NH_2), 3.70 (3H, s, OCH_3), 4.88 (1H, d, *J* = 7.2, C*H*N), 6.76 (2H, app d, *J* = 9.0, C$H_{PMPC3-H}$), 6.85 (1H, dd, *J* = 5.1, 3.6, C$H_{thiophene}$), 6.95 (1H, dd , *J* = 3.6, 1.3, C$H_{thiophene}$), 7.12 (2H, app d, *J* = 8.9, C$H_{PMPC2-H}$), 7.18 (1H, d, *J* = 5.0, C$H_{thiophene}$); ^{13}C NMR (150 MHz) δ 11.0 (CH_2CH_3), 22.9 (CH_2), 51.2 ($CHCH_2$), 55.1 (OCH_3), 61.1 ($CHNH_2$), 67.1 (*C*HN), 113.7 (CH_{PMPC3}), 125.6 (CH_{PMPC2}), 125.8 ($CH_{thiophene}$), 126.6 ($CH_{thiophene}$), 126.8 ($CH_{thiophene}$), 130.0 (*C*q Arom.), 142.4 (*C*q Arom.), 157.2 (Cq_{PMPC4}), 173.9 (*C*=O); *m/z* (ESI^+) 317 (71%, $M+H^+$), 206 (100%); HRMS: found 317.1321, $C_{17}H_{21}N_2O_2S$ requires 317.1324; Anal. Cald. For $C_{17}H_{20}N_2O_2S$: C, 64.53, H, 6.37, N, 8.85. Found C, 64.68, H, 6.56, N, 8.77%.

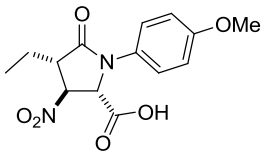
N-((2*R*, 3*R*, 4*R*)-4-ethyl-1-(4-methoxyphenyl)-5-oxo-2-(thiophen-2-yl)pyrrolidin-3-yl)-2,2,2-trifluoroacetamide 287



To a solution of amine **561** (127 mg, 0.410 mmol) in DCM (4 mL) at 0 °C, was added trifluoroacetic anhydride (280 µL, 2.05 mmol, 5 equiv.) followed by pyridine (160 µL, 2.05 mmol, 5 equiv.). The mixture was then warmed to rt and stirred for a further 2 h, then 2 M aqueous HCl (20 mL) and CH_2Cl_2 (20 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2x20 mL) and the combined organics washed with saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give crude trifluoroacetamide **287**. Purification by flash column chromatography (Petrol:Me_2CO 7:3) gave trifluoroacetamide **287** (136 mg, 82%) as a white solid; mp. 139-140 °C; R_f 0.46 (Petrol:Me_2CO 7:3); HPLC (chiralcel AD 0.46 x 25 cm column, 90:10 hexane/IPA, 1 mL min-1) 10.9 min (major), 20.4 min (minor) measured 87% *ee*; IR υ_{max} (thin film) 3257 br (N-H), 3089 w (C-H), 1720 m, 1672 s (C=O), 1515 m, 1254 m, 1212 m, 1168 s, 1030 m, 845 m, 693 s cm^{-1}; ^1H NMR (600 MHz) δ 0.96 (3H, t, *J* = 7.4, CH_3), 1.65 (1H, m, CH_2), 1.87 (1H, m, CH_2), 2.25 (1H, dt, *J* = 8.7, 5.5, C*H*Et), 3.74 (3H, s, OCH_3), 4.36 (1H, app dt, *J* = 8.7, 5.3, C*H*NHTFA), 5.18 (1H, d, *J* = 4.7, C*H*N), 6.81 (2H, app d, *J* = 8.9, $CH_{PMPC3-H}$), 6.85 (1H, m, $CH_{thiophene}$), 6.89 (1H, m, $CH_{thiophene}$), 7.15 (2H, app d, *J* = 8.9, $CH_{PMPC2-H}$), 7.19 (1H, d, *J* = 5.0 $CH_{thiophene}$), 8.26 (1H, d, *J* = 8.7, $CH_{PMPC2-H}$); ^{13}C NMR (150 MHz) δ 11.2 (CH_2CH_3), 23.7 (CH_2), 49.4 ($CHCH_2$), 55.3 (OCH_3), 56.9 (*C*HNHTFA), 65.0 (*C*HN), 114.1 (CH_{PMPC3}), 125.6 (CH_{PMPC2}), 115.7 (q, J^1_{C-F} = 288, CF_3), 126.0 ($CH_{thiophene}$),126.5 ($CH_{thiophene}$), 126.9 ($CH_{thiophene}$), 129.2 (*C*q Arom.), 141.3 (*C*q Arom.), 157.0 (q, J^1_{C-F}=288, CF_3C=O), 157.9 ($CqPMPC4$), 173.6 (N*C*=O); ^{19}F NMR (282 MHz) δ -76.0 (3F, s, CF_3); *m/z* (ESI^+) 413 (100%, $M+H^+$), 300 (30%, M^+-NHTFA); HRMS: found 413.1139, $C_{19}H_{20}F_3N_2O_3S$ requires 413.1147; Anal. Cald. For $C_{19}H_{19}F_3N_2O_3S$: C, 55.33, H, 4.64, N, 6.79. Found C, 55.24, H, 4.59, N, 6.69%.

Recrystallisation of the sample with Et_2O/hexane gave **287** (111 mg, 73% overall yield) as an identical white solid; $[\alpha]_D$ +14.7 (c 1, $CHCl_3$, 20 °C); HPLC measured 99% ee.

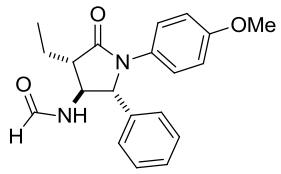
(2*S,3*S**,4*S**)-4-ethyl-1-(4-methoxyphenyl)-3-nitro-5-oxopyrrolidine-2-carboxylic acid 319**



To a solution of ethyl ester **242** (336 mg, 1.00 mmol) in acetone (11 mL) was added an aqueous solution of HCl (2 M, 10.0 mL, 20 equiv.) and the mixture was refluxed for 24 h. After the mixture was cooled, EtOAc (20 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (2x20 mL) and the combined organics extracted with saturated aqueous $NaHCO_3$ (2x10 mL). The combined aqueous extracts were then acidified to pH = 1 with addition of 2 M HCl and then extracted with EtOAc (3x20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give carboxylic acid **319** (265 mg, 86%) as a white solid; mp. 155-156 °C; R_f 0.34 (DCM:MeOH 9:1); IR υ_{max} (thin film) 2967 w (C-H), 2463 m, 1739 m (C=O), 1634 m (C=O), 1604 m, 1560 m (N=O), 1369 m (N-O), 1248 s, 1222 m, 1203 m, 1183 m, 1020 m, 792 m cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 1.13 (3H, t, *J* = 7.4, CH_2CH_3), 1.80 (1H, ddq, *J* = 14.2, 8.7, 7.4, CH_2CH_3), 2.00 (1H, dqd, *J* = 14.1, 7.4, 5.5, CH_2CH_3), 3.17 (1H, ddd, *J* = 8.9, 5.5, 3.7, $CHCH_2$), 3.79 (3H, s, OCH_3), 5.29 (1H, t, *J* = 3.3, $CHNO_2$), 5.34 (1H, d, *J* = 2.8, NC*H*), 6.95 (2H, app d, *J* = 8.9, $CH_{PMPC3\text{-}H}$), 7.36 (2H, app d, *J* = 8.9, $CH_{PMPC2\text{-}H}$); ^{13}C NMR (150 MHz, CD_3OD) δ 11.5 (CH_3), 24.5 (CH_2), 51.0 ($CHCH_2$), 55.9 (OCH_3), 66.1 (N*C*H), 85.4 ($CHNO_2$), 115.3 (CH_{PMPC3}), 127.1 (CH_{PMPC2}), 130.9 (Cq_{PMPC1}), 160.0 (Cq_{PMPC4}), 171.4 (N*C*=O), 174.4 (O*C*=O); *m/z* (CI^+) 309 (100%, $M+H^+$), 218 (40%, $M^+ - CO_2 - NO_2$); HRMS: found 309.10666, $C_{14}H_{17}N_2O_6$ requires 309.10872; Anal. Cald. For $C_{14}H_{16}N_2O_6$: C, 54.54, H, 5.23, N, 9.09. Found C, 54.21, H, 5.19, N, 8.96%.

Also prepared by reaction of **242** with Me_3SnOH.[159] To a solution of ethyl ester **242** (161 mg, 0.48 mmol) in 1,2-dichloroethane (5 mL) was added Me_3SnOH (174 mg, 0.92 mmol) and the mixture was heated at reflux (80 °C) until complete consumption of the ethyl ester (TLC, 5 h). EtOAc (15 mL) was then added and the mixture washed with brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude acid **319**. Purification by flash column chromatography (DCM:MeOH 9:1) gave acid **319** (100 mg, 68%) identical to the one reported above.

_N_-((2_R_*, 3_S_*, 4_S_*)-4-ethyl-1-(4-methoxyphenyl)-5-oxo-2-phenylpyrrolidin-3-yl)formamide 312[254]

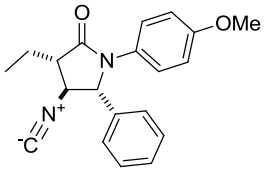


To a solution of amine **246** (250 mg, 0.810 mmol) in formic acid (5 mL) at 0 °C was added dropwise acetic anhydride (810 μL, 8.06 mmol, 10 equiv.). The mixture was then stirred at rt for 2 h. Water (20 mL) was then added and the mixture extracted with DCM (3x20 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (2x20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give crude formamide **312**. Purification by flash column chromatography (Petrol:Me_2CO 7:3) gave formamide **312** (246 mg, 90%) as a white crystalline solid which was found to be a mixture of rotamers at a ratio of 80:20; rotamer ratio calculated by C*H*NH signal, δ major = 4.24, δ minor = 3.67; mp. 130-131 °C; R_f 0.16 (Petrol:Me_2CO 7:3); Major rotamer: IR υ_{max} (thin film) 3239 br. (N-H), 3059 w (C-H), 2961 w (C-H), 1704 s (C=O), 1644 s (C=O), 1510 s, 1374 m, 1246 s, 1180 m, 1026 m, 834 m, 749 m, 737 m, 698 cm^{-1}; ^1H NMR (600 MHz) δ 1.03 (3H, t, *J* = 7.5, CH_2CH_3), 1.62 (1H, m, CH_2CH_3), 1.91 (1H, m, CH_2CH_3), 2.53 (1H, m, $CHCH_2$), 3.73 (3H, s, OCH_3), 4.24 (1H, dt, *J* = 7.8, 5.7, C*H*NH), 5.05 (1H, d, *J* = 4.9, NC*H*), 6.37 (1H, d, *J* = 8.4, N*H*), 6.75 (2H, app. d, *J* = 9.2, $CH_{PMPC3\text{-}H}$), 7.10-7.31 (7H, m, C*H* Arom.), 8.18 (1H, d, *J* = 1.2, O=C*H*); ^{13}C NMR (150 MHz) δ 11.5 (CH_3), 23.4 (CH_2), 50.3 ($CHCH_2$), 55.3 (OCH_3), 56.0 (*C*HNH), 68.6 (N*C*H), 114.0 (CH_{PMPC3}), 124.3 (*C*H Arom.), 126.7 (*C*H Arom.), 128.2 (*C*H Arom.), 128.9 (*C*H Arom.), 130.4 (*C*q Arom.), 138.3 (*C*q Arom.), 157.0 (Cq_{PMPC4}), 160.9 (O=*C*H), 174.1 (*C*=O); *m/z* (CI^+) 339 ($M+H^+$, 30%), 294 (100%, M^+ - NHCOH); HRMS: found 339.1699, $C_{20}H_{23}N_2O_3$ requires 339.1709.

Minor rotamer: ^1H NMR (600 MHz) δ 1.10 (3H, t, *J* = 7.4, CH_2CH_3), 1.62 (1H, m, CH_2CH_3), 1.91 (1H, m, CH_2CH_3), 2.53 (1H, m, $CHCH_2$), 3.67 (1H, m, C*H*NH), 3.71 (3H, s, OCH_3), 4.76 (1H, d, *J* = 7.7, NC*H*), 6.30 (1H, t, *J* = 10.8, N*H*), 6.78 (2H, app d, *J* = 9.2, $CH_{PMPC3\text{-}H}$), 7.10-7.31 (7H, m, C*H* Arom.), 7.62 (1H, d, *J* = 11.5, O=C*H*); ^{13}C NMR (150 MHz) δ 10.8 (CH_3), 21.6 (CH_2), 48.8 ($CHCH_2$), 55.3 (OCH_3), 60.9 (*C*HNH), 68.4 (N*C*H), 113.9 (CH_{PMPC3}), 124.9 (*C*H Arom.), 127.0 (*C*H Arom.), 128.7

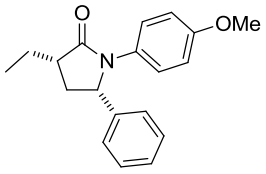
(*C*H Arom.), 129.2 (*C*H Arom.), 129.7 (*C*q Arom.), 136.7 (*C*q Arom.), 157.2 (Cq_{PMPC4}), 163.7 (O=*C*H), 172.5 (*C*=O).

(3*S,4*S**,5*R**)-3-ethyl-4-isocyano-1-(4-methoxyphenyl)-5-phenylpyrrolidin-2-one 313**[254]



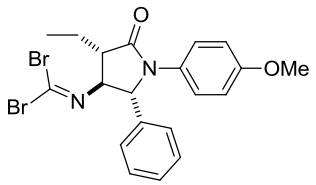
To a solution of formamide **312** (441 mg, 1.31 mmol) in THF (4 mL) at -78 °C, was added Et_3N (920 µL, 6.53 mmol, 5 equiv.) followed by a solution of $POCl_3$ (160 µL, 1.55 mmol, 1.18 equiv.) in THF (1 mL) dropwise. The mixture was then warmed to 0 °C and stirred for a further 1 h. Ice-water (20 mL) was then added and the mixture extracted with EtOAc (4x30 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give crude isocyanide **313**. Purification by flash column chromatography (Petrol:Me_2CO 4:1) gave isocyanide **313** (261 mg, 63%) as a white crystalline solid; mp. 168-169 °C; R_f 0.26 (Petrol:Me_2CO 4:1); IR υ_{max} (thin film) 2970 w (C-H), 2141 m (C≡N), 1707 s, 1509 s, 1458 m, 1365 m, 1247 s, 1223 m, 1193 m, 1179 m, 1039 m, 830 s, 784 m, 742 s, 700 s cm^{-1}; ^{1}H NMR (600 MHz) δ 1.16 (3H, t, *J* = 7.5, CH_3), 1.83 (1H, m, CH_2), 2.12 (1H, dqd, *J* = 12.4, 7.6, 4.7, CH_2), 2.92 (1H, ddd, *J* = 9.4, 7.9, 4.7, C*H*CH_2), 3.71 (3H, s, OCH_3), 3.79 (1H, dd, *J* = 9.4, 7.6, C*H*N≡C), 5.10 (1H, d, *J* = 7.6, C*H*Ph), 6.77 (2H, app d, *J* = 9.0, $CH_{PMPC3\text{-}H}$), 7.15 (2H, app d, *J* = 9.0, $CH_{PMPC2\text{-}H}$), 7.22-7.35 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 10.7 (CH_2CH_3), 22.5 (CH_2), 50.0 (*C*HCH_2), 55.2 (OCH_3), 59.9 (*C*HN≡C), 67.4 (*C*HPh), 114.0 (CH_{PMPC3}), 125.0 (CH_{PMPC2}), 126.8 (*C*H Arom.), 129.0 (*C*H Arom.), 129.2 (*C*H Arom.), 129.2 (*C*q Arom.), 136.4 (*C*q Arom.), 157.3 (Cq_{PMPC4}), 160.2 (-N≡*C*), 171.2 (*C*=O); *m/z* (EI^+) 320 (M^+, 100%); HRMS: found 320.15222, $C_{20}H_{20}N_2O_2$ requires 320.15193; Anal. Cald. For $C_{20}H_{20}N_2O_2$: C, 74.98, H, 6.29, N, 8.74. Found C, 74.94, H, 6.27, N, 8.68%.

(3*S, 5*S**)-3-ethyl-1-(4-methoxyphenyl)-5-phenylpyrrolidin-2-one 311**



To a solution of isocyanide **313** (56 mg, 0.18 mmol) in Toluene (1 mL) was added $^{n}Bu_3SnH$ (100 μL, 0.320 mmol, 2 equiv.). The mixture was degassed with N_2 and then AIBN (6 mg, 0.04 mmol, 20 mol %) was added and the mixture refluxed for 3 h. The volatiles were then removed *in vacuo* to give crude pyrrolidine **311**. Purification by flash column chromatography (Petrol:Et_2O 1:1) gave pyrrolidine **311** (45 mg, 87%) as a white solid; mp. 97-98 °C; R_f 0.19 (Petrol:Et_2O 1:1); IR υ_{max} (thin film) 2956 w (C-H), 1689 s (C=O), 1510 s, 1380 m, 1361 m, 1298 m, 1249 s, 1175 m, 1034 m, 829 s, 761 m, 699 s cm^{-1}; ^1H NMR (600 MHz) δ 1.03 (3H, t, *J* = 7.5, C*H*$_3$), 1.59 (1H, ddq, *J* = 14.0, 9.2, 7.3, C*H*$_2$CH$_3$), 1.67 (1H, ddd, *J* = 12.9, 10.5, 8.9, CHC*H*$_2$CH), 2.10 (1H, dqd, *J* = 14.1, 7.5, 4.1, C*H*$_2$CH$_3$), 2.62 (1H, ddd, *J* = 10.4, 9.0, 4.1, C*H*CH$_2$), 2.76 (1H, ddd, *J* = 12.9, 8.8, 7.1, CHC*H*$_2$CH), 3.71 (3H, s, OC*H*$_3$), 5.10 (1H, dd, *J* = 8.8, 7.1, C*H*Ph), 6.75 (2H, app d, *J* = 8.9, C*H*$_{PMPC3-H}$), 7.17-7.29 (7H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 11.5 (CH$_2$*C*H$_3$), 24.5 (*C*H$_2$CH$_3$), 36.2 (CH*C*H$_2$CH), 44.0 (*C*HEt), 55.2 (O*C*H$_3$), 62.2 (*C*HPh), 113.7 (*C*H$_{PMPC3}$), 124.7 (*C*H$_{PMPC2}$), 126.6 (*C*H Arom.), 127.6 (*C*H Arom.), 128.7 (*C*H Arom.), 130.9 (*C*q$_{PMPC1}$), 141.4 (*C*q$_{phenylC1}$), 156.7 (*C*q$_{PMPC4}$), 176.5 (*C*=O); *m/z* (EI$^+$) 295 (M$^+$, 100%); HRMS: found 295.15751, $C_{19}H_{21}NO_2$ requires 295.15667; Anal. Cald. For $C_{19}H_{21}NO_2$: C, 77.26, H, 7.17, N, 4.74. Found C, 77.19, H, 7.21, N, 4.79%.

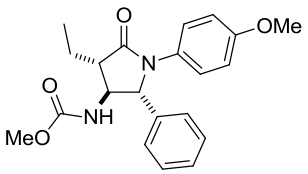
((2*R,3*S**,4*S**)-4-Ethyl-1-(4-methoxyphenyl)-5-oxo-2-phenylpyrrolidin-3-yl)carbonimidic dibromide 314**[148]



To a stirred solution of bromine (14 μL, 0.27 mmol) in MeOH (3 mL) was added a solution of isocyanide **313** (87 mg, 0.27 mmol) in MeOH (1 mL) at 0 ^oC over 30 min.

The mixture was stirred at this temperature for a further 30 min and then at rt until consumption of the starting isocyanide (TLC, 3.5 h). The mixture was then added to a stirred suspension of $CaCO_3$ (100 mg) in water (30 mL) and stirred for 2 h. The precipitate was filtered off and the filtrate extracted with DCM (3x10 mL), the combined organics then washed with H_2O (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude pyrrolidinone **314**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone **314** (85 mg, 65%) as a yellow solid; mp. 240 °C (decomposition); R_f 0.42 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2965 w (C-H), 2932 w (C-H), 1698 m (C=O), 1669 m, 1599 s, 1572 m, 1510 s, 1439 s, 1357 s, 1295 m, 1184 m, 1033 m, 831 m, 796 m, 751 m, 699 s cm^{-1}; ^{1}H NMR (600 MHz) δ 1.08 (3H, t, *J* = 7.5, C*H*$_3$), 1.79 (1H, m, C*H*$_2$CH$_3$), 1.95 (1H, m, C*H*$_2$CH$_3$), 2.91 (1H, m, C*H*CH$_2$), 3.71 (3H, s, OC*H*$_3$), 3.96 (1H, dd, *J* = 8.1, 6.7, C*H*N=), 5.05 (1H, d, *J* = 6.5, PhC*H*N), 6.76 (2H, app d, *J* = 8.7, C*H*$_{PMPC3-H}$), 7.11-7.32 (7H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 11.0 (CH$_2$*C*H$_3$), 22.1 (*C*H$_2$CH$_3$), 49.4 (*C*HCH$_2$), 55.2 (O*C*H$_3$), 66.1 (*C*HPh), 75.9 (*C*HN=), 94.3 (=*C*Br$_2$), 113.9 (*C*H$_{PMPC3}$), 124.7 (*C*H Arom.), 126.9 (*C*H Arom.), 128.3 (*C*H Arom.), 129.0 (*C*H$_{PMPC2}$), 130.0 (*C*q Arom.), 137.3 (*C*q Arom.), 157.0 (*C*q$_{PMPC4}$), 173.2 (*C*=O); *m/z* (CI$^+$) 482 (M$^+$ Br^{81}Br^{81}, 52%), 480 (M$^+$ Br^{79}Br^{81}, 100%), 478 (M$^+$ Br^{79}Br^{79}, 51%), 436 (77%), 320 (M$^+$-Br$_2$, 47%), 294 (32); HRMS: found 477.98752, $C_{20}H_{20}Br_2N_2O_2$ requires 477.98860.

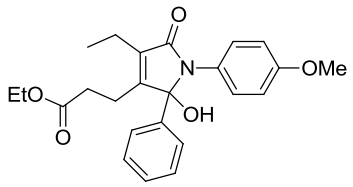
Methyl-((2*R,3*S**,4*S**)-4-ethyl-1-(4-methoxyphenyl)-5-oxo-2-phenylpyrrolidin-3-yl)carbamate 315**[148]



To a stirred solution of bromine (24 μL, 0.86 mmol) in MeOH (1 mL) was added a solution of isocyanide **313** (138 mg, 0.430 mmol) in MeOH (6 mL) and THF (2 mL) at 0 °C over 30 min. The mixture was warmed to rt, stirred until consumption of the starting isocyanide (TLC, 2 h) and then heated at reflux until the intermediate pyrrolidinone **314** was consumed (TLC, 15 h). The mixture was then added to a stirred suspension of $CaCO_3$ (100mg) in water (30 mL) and stirred for 2 h. The precipitate was filtered off and the filtrate extracted with DCM (3x10 mL), the

combined organics then washed with H_2O (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude pyrrolidinone **315**. Purification by flash column chromatography (Petrol:EtOAc 1:1) gave pyrrolidinone **315** (66 mg, 42%) as a white solid; mp. 165-166 °C; R_f 0.31 (Petrol:EtOAc 1:1); IR υ_{max} (thin film) 3317 br (N-H), 2933 w (C-H), 1771 m, 1689 s (C=O), 1513 s, 1498 m, 1378 m, 1250 s, 1182 m, 1037 m, 701 m cm^{-1}; ^1H NMR (600 MHz, at 60 °C) δ 1.10 (3H, t, *J* = 7.6, C*H*$_3$), 1.72 (1H, m, C*H*$_2$CH$_3$), 1.97 (1H, m, C*H*$_2$CH$_3$), 2.59 (1H, m, C*H*CH$_2$), 3.67 (3H, s, O=COC*H*$_3$), 3.74 and 3.82 (3H, s, ArOC*H*$_3$), 3.96 (1H, m, C*H*NH), 4.92 (1H, m, N*H*), 5.00 (1H, m, C*H*Ph), 6.78 (2H, app d, *J* = 8.7, C*H*$_{PMPC3-H}$), 7.20-7.35 (7H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 11.4 (CH$_2$*C*H$_3$), 23.0 (*C*H$_2$CH$_3$), 49.8 and 50.1 (*C*HCH$_2$), 52.4 (O=CO*C*H$_3$), 55.3 and 56.3 (O*C*H$_3$), 58.9 (*C*HNH), 68.4 (*C*HPh), 111.4, 113.9, 124.2, 126.7, 126.8, 128.1, 128.8, 128.9 (*C*H Arom.), 130.6 (*C*q Arom.), 138.5 (*C*q Arom.), 156.2 (*C*q$_{PMPC4}$), 156.8 (O*C*=O), 173.8 (CH*C*=O); *m/z* (ESI$^+$) 369 (M+H$^+$, 100%), 294 (M$^+$-CH$_3$CONH, 85%); HRMS: found 369.1799, $C_{21}H_{24}N_2O_4$ requires 369.1814.

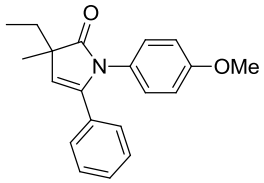
Ethyl 3-(4-ethyl-2-hydroxy-1-(4-methoxyphenyl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)propanoate 303[145]



To a solution of pyrrolidinone **233** (213 mg, 0.630 mmol) in wet MeCN (6 mL) at rt was added ethyl acrylate (103 μL, 0.950 mmol) followed by DBU (141 μL, 0.950 mmol). The mixture was then stirred at rt for 24 h, then evaporated *in vacuo*. Purification by flash column chromatography (Petrol:Me$_2$CO 4:1) gave pyrrolidinone **303** (128 mg, 50%) as a white solid; mp. 99-100 °C; R_f 0.19 (Petrol:Me$_2$CO 4:1); IR υ_{max} (thin film) 3318 br (O-H), 2967 w (C-H), 2939 w (C-H), 2877 w, 1731 s (C=O), 1658 s, 1509 s, 1449 m, 1372 s, 1244 s, 1183 s, 1172 s, 1030 m, 828 s, 700 m cm^{-1}; ^1H NMR (600 MHz) δ 1.16 (3H, t, *J* = 7.6, CCH$_2$C*H*$_3$), 1.27 (3H, t, *J* = 7.1, OCH$_2$C*H*$_3$), 2.29 (1H, m, CC*H*$_2$CH$_2$), 3.39 (2H, m, C*H*$_2$CH$_3$), 3.54 (3H, m, CC*H*$_2$CH$_2$ and CH$_2$C*H*$_2$CO), 3.71 (3H, s, OC*H*$_3$), 4.15 (2H, q, *J* = 7.3, OC*H*$_2$CH$_3$), 5.02 (1H, s, O*H*), 6.72 (2H, d, *J* = 9.2, C*H*$_{PMPC3-H}$), 7.20-7.32 (5H, m, C*H* Arom.), 7.39 (2H, m,

C*H*$_{PMPC2-H}$); ^{13}C NMR (150 MHz) δ 13.2 (CH_2CH_3), 14.1 (OCH_2CH_3), 17.2 (CCH_2CH_3), 20.3 (CH_2CH_2CO), 32.1 (CH_2CH_2CO), 55.2 (OCH_3), 93.3 (*C*qOH), 113.7 (*C*H$_{PMPC3}$), 126.1, 126.3, 128.2, 128.5 (Arom. *C*-H), 129.1 (*C*q$_{PMPC1}$), 135.4 (=*C*qCO), 137.9 (*C*q$_{phenyl}$), 152.5 (=*C*qCH_2), 157.1 (*C*q$_{PMPC4}$), 169.7 (N*C*=O), 173.9 (EtO*C*=O); *m/z* (ESI$^-$) 408 (M-H, 100%), 308 (40%, M-$C_5H_8O_2$); HRMS: found 408.1796, $C_{24}H_{26}NO_5$ requires 408.1811; Anal. Cald. For $C_{24}H_{26}NO_5$: C, 70.40, H, 6.65, N, 3.42. Found C, 70.08, H, 6.67, N, 3.42%.

3-Ethyl-1-(4-methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrrol-2(3*H*)-one 310



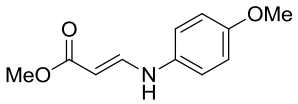
A solution of $^{i}Pr_2NH$ (33 μL, 0.24 mmol) in THF (2 mL) was cooled to -78 ^{o}C and ^{n}BuLi (12 μL, 2.10 M in hexanes, 0.24 mmol) was added. The mixture was then warmed to rt and stirred for 30 min. The mixture was recooled to -78 ^{o}C and a solution of pyrrolidinone **233** (70 mg, 0.20 mmol) in THF (2 mL) was added, the mixture stirred for 30 min before MeI (37 μL, 0.60 mmol) was added. The mixture was stirred for 10 min, then warmed to rt and stirred for a further 3 h. Saturated aqueous $NaHCO_3$ (10 mL) was then added and the mixture extracted with DCM (3x10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give crude pyrrolone **310**. Purification by flash column chromatography (Petrol:Me_2CO 4:1) gave pyrrolone **310** (13 mg, 21%) as a yellow solid; mp. 71-73 ^{o}C; R_f 0.42 (Petrol:Me_2CO 4:1); IR υ_{max} (thin film) 2964 w (C-H), 2930 w, 1718 s (C=O), 1511 s, 1248 s, 1177 w, 1032 w, 697 w cm^{-1}; ^{1}H NMR (600 MHz) δ 0.91 (3H, t, *J* = 7.3, CH_2CH_3), 1.36 (3H, s, CH_3), 1.70 (1H, dq, *J* = 14.9, 7.5, CH_2CH_3), 1.86 (1H, dq, *J* = 14.9, 8.4, CH_2CH_3), 3.78 (3H, s, OCH_3), 5.47 (1H, s, =C*H*), 6.81 (2H, d, *J* = 9.0, C*H*$_{PMPC3-H}$), 6.97 (2H, d, *J* = 9.0, C*H*$_{PMPC2-H}$), 7.14 (2H, m, C*H* Arom.), 7.24 (3H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 9.2 (CH_2CH_3), 22.4 (CCH_3), 31.0 (CH_2CH_3), 50.7 (*C*q), 55.4 (OCH_3), 113.9 (=*C*H), 114.0 (*C*H$_{PMPC3}$), 127.6 (*C*H Arom.), 128.0 (*C*H Arom.), 128.1 (*C*H Arom.), 128.3 (*C*H Arom.), 128.7 (=*C*-Ph), 131.4 (*C*q$_{PMPC1}$), 143.4 (*C*q$_{phenyl}$), 158.0 (*C*q$_{PMPC4}$), 182.7 (*C*=O); *m/z* (EI$^+$)

307 (M^+, 27%), 278 (100%, M^+-Et); HRMS: found 307.1554, $C_{20}H_{21}NO_2$ requires 307.1567; Anal. Cald. For $C_{20}H_{21}NO_2$: C, 78.15, H, 6.89, N, 4.56. Found C, 77.68, H, 6.91, N, 4.53%.

3.4.2 Towards the synthesis of a human neutrophil elastase inhibitor (GW311616A)

3.4.2.1 Synthesis of starting materials

(E)-Methyl 3-((4-methoxyphenyl)amino)acrylate 345



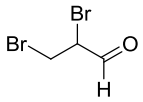
To a solution of methyl 3-oxopropanoate (520 mg, 5.10 mmol) in dry DCM (30 mL) were added 4 Å molecular sieves (10 g) followed by *para*-anisidine (615 mg, 5.00 mmol) and the mixture was stirred at rt for 20 h. The mixture was then filtered through celite® and washed with DCM (20 mL). The filtrate was concentrated *in vacuo* to give crude enamine **345** (701 mg, 66%) which was recrystallised from Et_2O to give pure enamine **345** (169 mg, 16 %) as a yellow oil; IR υ_{max} (thin film) 2951 w (C-H), 1731 m (C=O), 1670 m, 1609 m, 1510 s, 1435 s, 1227 s, 1176, 1030 s, 822 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.71 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 5.15 (1H, d, *J* = 13.2, O=CC*H*), 6.58 (1H, d, *J* = 13.2, N*H*), 6.86 (2H, app. d, *J* = 8.8, C*H*$_{PMPC3-H}$), 6.92 (2H, app. d, *J* = 8.8, C*H*$_{PMPC2-H}$), 7.83 (1H, t, *J* = 12.9, N=C*H*); ^{13}C NMR (125 MHz) δ 50.8 (OCO*C*H$_3$), 55.6 (ArO*C*H$_3$), 90.7 (OC*C*=), 114.9 (*C*H$_{PMPC3}$), 117.8 (*C*H$_{PMPC2}$), 133.9 (*C*q$_{PMPC1}$), 144.2 (N=*C*H), 155.6 (*C*q$_{PMPC4}$), 169.5 (*C*=O); *m/z* (ES$^-$) 206 (M-H$^+$, 100%); HRMS: found 206.0803, $C_{11}H_{12}NO_3$ requires 206.0817.

3,3-Dimethoxypropanal 347 and (*E*)-3-methoxyacrylaldehyde 349[255]

A 250 mL round bottom flask was charged with methyl 3,3-dimethoxypropionate (7.00 mL, 50.0 mmol) and dry hexane (100 mL). The mixture was then cooled to -78

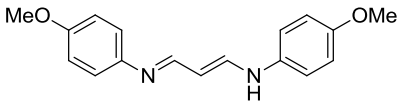
^{o}C and a solution of DIBAL (51.5 mL, 51.5 mmol, 1 M in DCM) cooled to -78 ^{o}C was added dropwise *via* cannula. The mixture was stirred at this temperature for 1 h and then quenched by addition of MeOH (5 mL) and stirred for 15 min. Saturated Rochelle salt solution (100 mL) was then added and the mixture stirred for 1 h at rt. The aqueous phase was then separated and extracted with petrol (35 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (Petrol:DCM 2:8) gave an inseparable mixture of the two products **347** and **349** in the ratio of 70:30 (combined yield: 66%) as a colourless liquid; R_f 0.53 (Petrol:DCM 2:8); 3,3-dimethoxypropanal **347** (major): ^{1}H NMR (600 MHz) δ 2.74 (2H, dd, *J* = 5.5, 2.2, C*H*$_2$), 3.39 (6H, s, OC*H*$_3$), 4.86 (1H, t, *J* = 5.3, C*H*(OCH$_3$)$_2$), 9.76 (1H, *t*, J = 2.2, C*H*O); ^{13}C NMR (125 MHz) δ 47.1 (*C*H$_2$), 53.7 (O*C*H$_3$), 100.3 (*C*H(OCH$_3$)$_2$), 199.5 (*C*HO). Data in agreement to that reported.[256] (*E*)-3-methoxyacrylaldehyde **349** (minor): ^{1}H NMR (600 MHz) δ 3.79 (3H, s, OC*H*$_3$), 5.62 (1H, dd, *J* = 12.7, 8.1, OCC*H*=), 7.42 (1H, d, *J* = 12.7, MeOC*H*=), 9.40 (1H, d, *J* = 8.1, C*H*O); ^{13}C NMR (125 MHz) δ 57.9 (*C*H$_3$), 109.6 (O=C*C*H), 171.1 (OC*C*H=), 191.2 (*C*HO). Data in agreement to that reported.[256]

2,3-Dibromopropanal 359



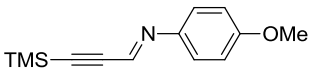
To a solution of acrolein (130 μL, 2.00 mmol) in dry DCM (10 mL) was added Br_2 (110 μL, 2.20 mmol) at rt. The solution was instantly decolorized and the mixture was evaporated *in vacuo* to give pure 2,3-dibromopropanal **359** (415 mg, 96%) as a colourless oil; ^{1}H NMR (600 MHz) δ 3.73 (1H, dd, *J* = 10.6, 4.7, C*H*$_2$), 3.88 (1H, t, *J* = 10.5, C*H*$_2$), 4.54 (1H, ddd, *J* = 10.4, 4.5, 2.7, C*H*Br), 9.39 (1H, d, *J* = 2.7, O=C*H*); ^{13}C NMR (150 MHz) δ 26.8 (*C*H), 48.8 (*C*H$_2$), 189.0 (*C*=O). Data in agreement to the one reported.[174]

(*E*)-4-methoxy-*N*-((*E*)-3-((4-methoxyphenyl)amino)allylidene)aniline 350



Prepared by general procedure A. The mixture of aldehydes **347** and **349** (11.5 mmol) in DCM (60 mL), *para*-anisidine (1.42 g, 11.5 mmol) and basic Al_2O_3 (11 g) afforded **350** (1.58 g, 97% based on *para*-anisidine) as a yellow solid which was used without further purification; mp. 122-123 ^oC (lit. 124 ^oC);[257] IR υ_{max} (thin film) 3199 w (N-H), 2952 w (C-H), 1629 s (C=O), 1594 s, 1574 s, 1502 w, 1305 s, 1279 s, 1246 s, 1233 s, 1156 s, 1031 m, 1007 m, 963 m, 830 s, 807 s cm^{-1}; ^1H NMR (600 MHz) δ 3.81 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.27 (1H, dd, J = 7.4, 2.1, CH_2CH_3), 6.89 (4H, m, C*H* Arom.), 7.02-7.05 (4H, m, C*H* Arom.), 7.64 (1H, d, *J* = 6.1, =C*H*), 9.27 (1H, dd, *J* = 3.2, 2.1, N=CH), 11.72 (1H, br. s, N*H*); ^{13}C NMR (150 MHz) δ 55.5 (O*C*H_3), 97.0 (=*C*HC), 114.6 (*C*H Arom.), 114.9 (*C*H Arom.), 118.1 (*C*H Arom.), 119.2 (*C*H Arom.), 133.4 (*C*q Arom.), 140.3 (*C*q Arom.), 148.0 (=CHN), 156.1 (*C*q Arom.), 156.6 (*C*q Arom.), 189.1 (N=*C*H); *m/z* (EI^+) 282 (M^+, 100%), 267 (33%); HRMS: found 282.13588, $C_{17}H_{18}N_2O_2$ requires 282.13627.

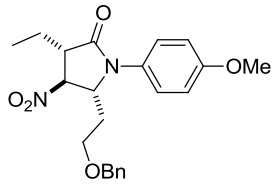
(*E*)-4-methoxy-*N*-(3-(trimethylsilyl)prop-2-yn-1-ylidene)aniline 356



To a solution of *para*-anisidine (123 mg, 1.00 mmol) in DCM (5 mL) was added dried $MgSO_4$ (700 mg) and the mixture cooled to 0 ^oC. 3-(trimethylsilyl)-2-propynal (0.150 mL, 1.00 mmol) was then added and the mixture stirred for 5 min at this temperature and then warmed to rt and stirred for a further 1 h, then filtered through celite® and washed with DCM (10 mL) and concentrated *in vacuo* to give imine **356** (226 mg, 98%, lit. 56%) as a yellow oil which was used without further purification; R_f 0.47 (Petrol:EtOAc 9:1); ^1H NMR (600 MHz) δ 0.27 (9H, s, Si*C*H_3), 3.83 (3H, s, O*C*H_3), 6.90 (2H, app. d, *J* = 9.0, *CH*$_{PMPC3-H}$), 7.20 (2H, app. d, *J* = 9.0, *CH*$_{PMPC2-H}$), 7.72 (1H, s, C*H*O). Data in agreement with that reported.[258]

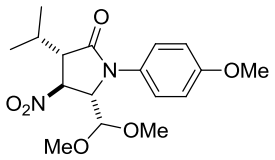
3.4.2.2 Investigation of methodology

(3*S,4*S**,5*R**)-5-(2-(benzyloxy)ethyl)-3-ethyl-1-(4-methoxyphenyl)-4-nitropyrrolidin-2-one 355**



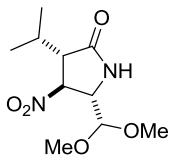
Prepared by general procedure C, with the exception that imine **352** was formed and used *in situ*. To a solution of aldehyde **353** (226 mg, 1.38 mmol) in THF (5 mL) were added under Nitrogen dried 4Å molecular sieves (1.40 g) and the mixture cooled at -78 ^{o}C. A solution of *para*-anisidine (170 mg, 1.38 mmol) in THF (1 mL) was then added and the mixture stirred at this temperature for 1.5 h. The solution was then transferred into the reaction *via* cannula. Nitroalkene **231** (100 mg, 0.690 mmol), diethylzinc (760 µL, 0.760 mmol), freshly prepared cold (-78 ^{o}C) solution of above-formed imine (1.38 mmol) and TFA (183 µL, 2.41 mmol) afforded crude pyrrolidinone **355**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone **355** (69 mg, 25%) as a colourless oil; R_f 0.23 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2934 w (C-H), 2967 w (C-H), 1702 s (C=O), 1554 s (N=O), 1511 s, 1455 w, 1366 m (N-O), 1296 w, 1248 s, 1180 w, 1098 m, 1030 m, 833 m, 740 m, 699 m cm^{-1}; ^{1}H NMR (600 MHz) δ 1.06 (3H, t, *J* = 7.4, CH_2CH_3), 1.76 (1H, m, CH_2CH_3), 1.76 (1H, m, $CHCH_2CH_2$), 2.03-2.13 (1H, m, CH_2CH_3), 2.03-2.13 (1H, m, $CHCH_2CH_2$), 3.12 (1H, m, $CHCH_2CH_3$), 3.43 (1H, m, OCH_2CH_2), 3.52 (1H, m, OCH_2CH_2), 3.80 (3H, s, OCH_3), 4.38 (1H, d, *J* = 11.8, OCH_2Ph), 4.42 (1H, d, *J* = 11.8, OCH_2Ph), 4.73 (1H, ddd, *J* = 9.2, 4.6, 3.2, $NCHCH_2$), 5.13 (1H, dd, *J* = 6.0, 4.6, $CHNO_2$), 6.92 (2H, app d, *J* = 9.0, $CH_{PMPC3-H}$), 7.21 (2H, app d, *J* = 9.0, $CH_{PMPC2-H}$), 7.23-7.40 (5H, m, C*H* Arom.); ^{13}C NMR (125 MHz) δ 10.8 (CH_2CH_3), 23.5 ($CHCH_2CH_3$), 32.3 ($CHCH_2CH_2$), 49.5 (*C*HEt), 55.4 (OCH_3), 60.8 ($CHCHCH_2$), 65.9 (CH_2CH_2O), 73.4 (OCH_2Ph), 87.0 ($CHNO_2$), 114.5 (CH_{PMPC3}), 126.3 (*C*H Arom.), 127.9 (*C*H Arom.), 128.4 (*C*H Arom.), 128.7 (*C*q Arom.), 137.3 (*C*q Arom.), 158.3 (Cq_{PMPC4}), 170.9 (*C*=O); *m/z* (EI^{+}) 398 (M^{+}, 30%), 260 (M^{+}-Bn-HNO_2, 10%), 217 (M^{+}-$BnOCH_2CH_2$-NO_2, 10%), 188 (10%), 91 ($C_6H_5CH_2^{+}$, 100%); HRMS found 398.18281, $C_{22}H_{26}N_2O_5$ requires 398.18361.

(3*S,4*S**,5*S**)-5-(dimethoxymethyl)-3-isopropyl-1-(4-methoxyphenyl)-4-nitropyrrolidin-2-one 361**



Prepared by general procedure C. Nitroalkene **231** (145 mg, 1.00 mmol), diisopropylzinc (3.09 mL, 0.356 M in hexane, 1.1 mmol), imine **267** (418 mg, 2.00 mmol) and TFA (270 μL, 3.50 mmol) afforded crude pyrrolidinone **361**. Purification by flash column chromatography (Petrol:Me_2CO 4:1) gave pyrrolidinone **361** (248 mg, 70%) as a white solid; mp. 145-146 ^oC; R_f 0.27 (Petrol:Me_2CO 4:1); IR υ_{max} (thin film) 2963 w (C-H), 2938 w (C-H), 2839 w (C-H), 1706 s (C=C), 1557 s, 1513 s, 1466 w, 1367 m, 1248 s, 1134 m, 1075 m, 1034 m, 836 w, 765 w cm^{-1}; ^1H NMR (600 MHz) δ 1.06 (3H, d, *J* = 7.0, CHC*H*$_3$), 1.13 (3H, d, *J* = 7.0, CHC*H*$_3$), 2.46 (1H, m, CHC*H*$(CH_3)_2$), 3.03 (1H, dd, *J* = 6.7, 4.8, C*H*$CH(CH_3)_2$), 3.33 (3H, s, OC*H*$_3$), 3.36 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 4.26 (1H, d, *J* = 2.6, CHC*H*$(OMe)_2$), 4.68 (1H, dd, *J* = 4.7, 2.6, C*H*$CH(OMe)_2$), 5.26 (1H, d, *J* = 6.6, 4.8, C*H*NO_2), 6.95 (2H, app. d, *J* = 8.9, C*H*$_{PMPC3-H}$), 7.26 (2H, app. d, *J* = 8.9, C*H*$_{PMPC2-H}$); ^{13}C NMR (125 MHz) δ 18.3 (*C*H_3), 19.6 (*C*H_3), 28.6 (*C*$H(CH_3)_2$), 54.0 (*C*$HCH(CH_3)_2$), 55.4 (O*C*H_3), 56.8 (O*C*H_3), 57.7 (O*C*H_3), 63.9 (*C*$HCH(OMe)_2$), 80.1 (*C*HNO_2), 102.6 (*C*$H(OMe)_2$), 114.6 (*C*H_{PMPC3}), 126.3 (*C*H_{PMPC2}), 128.8 (*C*q_{PMPC1}), 158.4 (*C*q_{PMPC4}), 170.8 (*C*=O); *m/z* (ES^+) 353 ($M+H^+$, 60%), 274 (M^+-NO_2-MeOH, 50%), 232 ($M+H^+$-NO_2-$CH(OMe)_2$, 100%); HRMS found 353.1706, $C_{17}H_{25}N_2O_6$ requires 353.1713; Anal. Cald. For $C_{17}H_{24}N_2O_6$: C, 57.94, H, 6.86, N, 7.95. Found C, 57.92, H, 6.86, N, 7.94%.

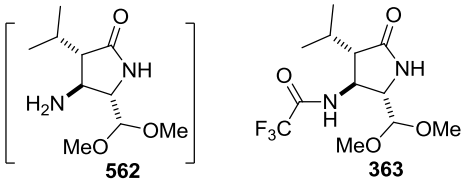
(3*S,4*S**,5*S**)-5-(dimethoxymethyl)-3-isopropyl-4-nitropyrrolidin-2-one 362**[116]



To a solution of pyrrolidinone **361** (107 mg, 0.300 mmol) in MeCN (4 mL) cooled to 0 ^oC was added a solution of CAN (658 mg, 1.20 mmol) in H_2O (4 mL) dropwise over 3 min. The solution turned from pale yellow to dark orange. The mixture was

stirred at this temperature for a further 2 h, over which the solution became light orange. Water (30 mL) was then added and the mixture extracted with EtOAc (3x20 mL), washed with saturated aqueous $NaHCO_3$ (40 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude pyrrolidinone **362**. Purification by flash column chromatography (Petrol:Me_2CO 7:3) gave pyrrolidinone **362** (61 mg, 83%) as a white solid; mp. 92-93 ^oC; R_f 0.33 (Petrol:Me_2CO 7:3); IR υ_{max} (thin film) 3223 br (N-H), 2964 m (C-H), 1709 s (C=O), 1557 s (N=O), 1466 w, 1370 m (N=O), 1133 m, 1074 m cm^{-1}; ^1H NMR (600 MHz) δ 0.95 (3H, t, *J* = 7.0, C*H*$_3$), 1.03 (3H, t, *J* = 7.0, C*H*$_3$), 2.35 (1H, m, C*H*$(CH_3)_2$), 3.03 (1H, dd, *J* = 7.2, 4.4, CHC*H*C=O), 3.42 (3H, s, OC*H*$_3$), 3.44 3.42 (3H, s, OC*H*$_3$), 4.17 (1H, dd, *J* = 6.1, 5.2, CHC*H*NH), 4.28 (1H, d, *J* = 6.1, C*H*$(OCH_3)_2$), 4.91 (1H, dd, *J* = 7.2, 5.2, C*H*NO_2), 6.94 (1H, br. s, N*H*); ^{13}C NMR (125 MHz) δ 18.0 (*C*H_3), 19.6 (*C*H_3), 27.5 (*C*H$(CH_3)_2$), 53.4 (CH*C*HC=O), 55.2 (O*C*H_3), 55.4 (O*C*H_3), 57.8 (CH*C*HNH), 83.0 (*C*HNO_2), 104.3 (*C*H$(OCH_3)_2$), 173.7 (*C*=O); *m/z* (ES^+) 247 ($M+H^+$, 100%), 215 (M^+-CH_3O, 30%), 168 (M^+-CH_3OH-NO_2, 92%); HRMS found 247.12907, $C_{10}H_{19}N_2O_5$ requires 247.12940; Anal. Cald. For $C_{10}H_{18}N_2O_5$: C, 48.77, H, 7.37, N, 11.38. Found C, 48.38, H, 7.40, N, 11.20%.

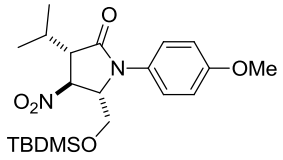
_N_-((2_S_*,3_S_*,4_S_*)-2-(dimethoxymethyl)-4-isopropyl-5-oxopyrrolidin-3-yl)-2,2,2-trifluoroacetamide 363



Diamine **562** produced by general procedure D. Pyrrolidinone **362** (326 mg, 1.33 mmol), HCl (6.60 mL, 40.0 mmol, 30.0 equiv.) and zinc dust (5.20 g, 80.0 mmol, 60.0 equiv.) afforded crude diamine **562**. To a solution of the crude diamine **562** (227 mg, 1.05 mmol) in DCM (10 mL) at 0 ^oC, was added trifluoroacetic anhydride (440 µL, 3.15 mmol, 3 equiv.) followed by pyridine (250 µL, 3.15 mmol, 3 equiv.). The mixture was then warmed to rt and stirred for a further 2 h. The mixture was then washed with aqueous 2 M HCl (2x20 mL), the combined organics washed with saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give crude trifluoroacetamide **363**. Purification by flash column chromatography

(Petrol:Me_2CO 7:3) gave trifluoroacetamide **363** (288 mg, 70%) as white needles; mp. 154-155 °C; R_f 0.27 (Petrol: Me_2CO 7:3); IR υ_{max} (thin film) 3281 br (N-H), 3094 br (N-H), 2962 w (C-H), 2934 (C-H), 1696 s (C=O), 1560 w, 1467 w, 1374 w, 1254 w, 1185 s, 1159 s, 1073 m, 961 w, 722 w cm^{-1}; ^1H NMR (600 MHz) δ 0.99 (3H, d, *J* = 6.8, CHCH_3), 1.00 (3H, d, *J* = 6.9, CHCH_3), 2.27 (1H, m, C*H*CH_3), 2.48 (1H, m, O=CC*H*CH), 3.44 (3H, s, OCH_3), 3.49 (3H, s, OCH_3), 3.51 (1H, m, C*H*NHCOCF_3), 4.29 (1H, d, *J* = 6.1, C*H*$(OMe)_2$), 4.45 (1H, m, NHC*H*CH$(OMe)_2$), 5.96 (1H, br. s, N*H*COCF_3), 6.87 (1H, m, N*H*C=O); ^{13}C NMR (150 MHz) δ 18.0 (*C*H_3), 20.1 (*C*H_3), 28.1 (*C*H$(CH_3)_2$), 48.8 (*C*HNHCOCF_3), 54.1 (O=C*C*HCH),55.6 (O*C*H_3), 56.5 (O*C*H_3), 60.1 (*C*HCH$(OMe)_2$), 107.4 (*C*H$(OMe)_2$), 117.4 (q, J = 286.8 Hz, *C*F_3), 158.0 (q, J = 37.1 Hz, O=*C*CF_3), 177.7 (O=*C*NH); ^{19}F NMR (282 MHz) δ -76.56 (3F, s, C*F*$_3$); *m/z* (CI^+) 313 ($M+H^+$, 42%), 281 (M^+-CH_3O, 100%), 217 (56%); HRMS: found 313.13721, $C_{12}H_{20}N_2O_4F_3$ requires 313.13752; Anal. Cald. For $C_{12}H_{19}N_2O_4F_3$: C, 46.15, H, 6.13, N, 8.97. Found C, 46.21, H, 6.15, N, 8.95%.

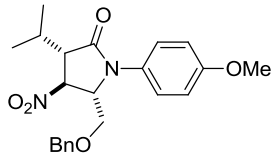
(3*S,4*S**,5*S**)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-isopropyl-1-(4-methoxyphenyl)-4-nitropyrrolidin-2-one 366**



Prepared by general procedure C, with the exception that imine **368** was formed and used *in situ*. To a solution of (*tert*-butyldimethylsiloxy)acetaldehyde (209 μL, 1.10 mmol) in THF (5 mL) were added under Nitrogen dried 4Å molecular sieves (1.10 g) and the mixture cooled at -78 °C. A solution of *para*-anisidine (135 mg, 1.10 mmol) in THF (1 mL) was added and the mixture stirred at this temperature for 1.5 h. The solution was then transferred into the reaction *via* cannula. Nitroalkene **231** (80 mg, 0.55 mmol), diisopropylzinc (1.74 mL, 0.356 M in hexane, 1.1 mmol), *in situ* prepared cold (-78 °C) solution of imine **368** (1.10 mmol) and TFA (140 μL, 1.93 mmol) afforded crude pyrrolidinone **366**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone **366** (31 mg, 13%) as a white solid; mp. 112-113 °C; R_f 0.50 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2957 w (C-H), 2931 w, 2858 w, 1704 s (C=C), 1556 m (N=O), 1513 s (C=O), 1464 m, 1408 w, 1366

m (N-O), 1298 m, 1249 s, 1108 m, 1037 m, 939 m, 837 s, 777 m cm^{-1}; ^1H NMR (600 MHz) δ -0.10 (3H, s, SiCH_3), -0.05 (3H, s, SiCH_3), 0.84 (9H, s, C(CH_3)$_3$), 1.03 (3H, d, *J* = 7.0, CH(CH_3)$_2$), 1.08 (3H, d, *J* = 7.0, CH(CH_3)$_2$), 2.49 (1H, m, C*H*(CH$_3$)$_2$), 3.36 (1H, dd, *J* = 7.9, 4.4, C=OC*H*), 3.68 (1H, dd, *J* = 11.3, 3.5, OCH_2), 3.75 (1H, dd, *J* = 11.3, 2.2, OCH_2), 3.81 (3H, s, OCH_3), 4.35 (1H, m, NC*H*), 5.22 (1H, dd, *J* = 7.9, 6.0, C*H*NO$_2$), 6.92 (2H, app. d, *J* = 8.9, CH_{PMPC3}), 7.18 (2H, app. d, *J* = 8.9, CH_{PMPC2}); ^{13}C NMR (125 MHz) δ -5.8 (Si*C*H$_3$), -5.8 (Si*C*H$_3$), 18.2 (CH(*C*H$_3$)$_2$), 19.6 (CH(*C*H$_3$)$_2$), 25.7 (C(*C*H$_3$)$_3$), 27.9 (*C*H(CH$_3$)$_2$), 52.3 (C=O*C*H), 55.3 (O*C*H$_3$), 59.5 (O*C*H$_2$), 63.3 (N*C*H), 81.1 (*C*HNO$_2$), 114.4 (*C*H$_{PMPC3}$), 126.8 (*C*H$_{PMPC2}$), 128.2 (*C*q$_{PMPC1}$), 158.5 (*C*q$_{PMPC4}$), 170.7 (*C*=O), 1 peak missing (*C*(CH$_3$)$_3$); *m/z* (ES$^+$) 423 (M+H$^+$, 75%), 376 (M$^+$-NO$_2$, 100%); HRMS found 423.2315, $C_{21}H_{35}N_2O_5Si$ requires 423.2315; Anal. Cald. For $C_{21}H_{34}N_2O_5Si$: C, 59.69, H, 8.11, N, 6.63. Found C, 59.68, H, 8.18, N, 6.57%.

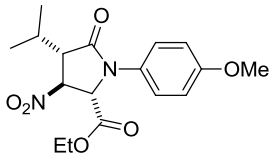
(3*S,4*S**,5*S**)-5-((benzyloxy)methyl)-3-isopropyl-1-(4-methoxyphenyl)-4-nitropyrrolidin-2-one 367**



Prepared by general procedure C, with the exception that imine **369** was formed and used *in situ*. To a solution of benzyloxyacetaldehyde (154 μL, 1.10 mmol) in THF (5 mL) were added under Nitrogen dried 4Å molecular sieves (1.10 g) and the mixture cooled at -78 ^oC. A solution of *para*-anisidine (135 mg, 1.10 mmol) in THF (1 mL) was then added and the mixture stirred at this temperature for 1.5 h. The solution was transferred into the reaction *via* cannula. Nitroalkene **231** (80 mg, 0.55 mmol), diisopropylzinc (1.74 mL, 0.356 M in hexane, 1.1 mmol), *in situ* prepared cold (-78 ^oC) solution of imine **369** (1.10 mmol) and TFA (140 μL, 1.93 mmol) afforded crude pyrrolidinone **367**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone **367** (68 mg, 31%) as a colourless oil; R_f 0.32 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2961 w (C-H), 1702 s (C=C), 1555 s (N-O), 1512 s (C=O), 1465 w, 1459 w, 1404 w, 1369 m (N-O), 1298 w, 1248 s, 1106 m, 1035 m, 834 m, 742 m, 699 m cm^{-1}; ^1H NMR (600 MHz) δ 0.96 (3H, d, *J* = 7.0, CH(CH_3)$_2$), 1.06 (3H, d, *J* = 7.0,

CH(CH_3)$_2$), 2.47 (1H, m, CH(CH$_3$)$_2$), 3.30 (1H, dd, J = 7.0, 4.5, C=OCH), 3.48 (1H, dd, J = 10.5, 4.0, OCH_2CH), 3.63 (1H, dd, J = 10.5, 2.5, OCH_2CH), 3.81 (3H, s, OCH_3), 4.39 (1H, d, J = 12.0, OCH_2Ph), 4.45 (1H, m, NCH), 4.48 (1H, d, J = 12.0, OCH_2Ph), 5.20 (1H, dd, J = 7.1, 5.3, CHNO$_2$), 6.91 (2H, app. d, J = 8.9, C$H_{PMPC3-H}$), 7.16 (2H, app. d, J = 8.9, C$H_{PMPC2-H}$), 7.20-7.36 (5H, m, CH Arom.); ^{13}C NMR (125 MHz) δ 18.1 (CH(*C*H$_3$)$_2$), 19.7 (CH(*C*H$_3$)$_2$), 28.1 (*C*H(CH$_3$)$_2$), 52.6 (C=O*C*H), 55.5 (O*C*H$_3$), 62.2 (N*C*H), 66.3 (O*C*H$_2$CH), 73.4 (O*C*H$_2$Ph), 81.7 (*C*HNO$_2$), 114.6 (*C*H$_{PMPC3}$), 127.1 (*C*H Arom.), 127.6 (*C*H Arom.), 128.0 (*C*H Arom.), 128.3 (*C*q$_{PMPC1}$), 128.4 (*C*H Arom.), 136.9 (*C*q Arom.), 158.6 (*C*q$_{PMPC4}$), 170.8 (*C*=O); *m/z* (ES$^+$) 399 (M+H$^+$, 55%), 352 (M$^+$-NO$_2$, 100%); HRMS found 399.1926, C$_{22}$H$_{27}$N$_2$O$_5$ requires 399.1920.

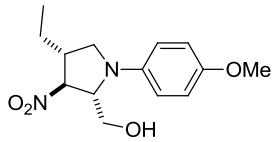
(2*S,3*S**,4*S**)-Ethyl 4-isopropyl-1-(4-methoxyphenyl)-3-nitro-5-oxopyrrolidine-2-carboxylate 373**



Prepared by general procedure C. Nitroalkene **231** (435 mg, 3.00 mmol), diisopropylzinc (9.27 mL, 0.356 M in hexane, 3.3 mmol), imine **24** (1.24 g, 6.00 mmol) and TFA (810 μL, 2.84 mmol) afforded crude pyrrolidinone **373**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave pyrrolidinone **373** (245 mg, 23%) as a yellow solid; mp. 40-41 ^{o}C; R$_f$ 0.38 (Petrol:EtOAc 4:1); IR υ$_{max}$ (thin film) 2965 w (C-H), 1745 m (C=O), 1712 s (C=O), 1561 s (N=O), 1513 s, 1371 m (N-O), 1299 m, 1248 m, 1197 m, 1029 m, 833 m cm^{-1}; ^{1}H NMR (600 MHz) δ 1.01 (3H, d, J = 7.0, CH(CH_3)$_2$), 1.14 (3H, d, J = 7.0, CH(CH_3)$_2$), 1.18 (3H, t, J = 7.1, CH$_2$CH_3), 2.45 (1H, m, CH(CH$_3$)$_2$), 3.14 (1H, t, J = 4.9, O=CCH), 3.80 (1H, s, OCH_3), 4.18 (2H, m, CH_2CH$_3$), 5.05 (1H, dd, J = 4.9, 3.7, CHNO$_2$), 5.18 (1H, d, J = 3.7, NCH), 6.92 (2H, app. d, J = 9.0, C$H_{PMPC3-H}$), 7.31 (2H, app. d, J = 9.0, C$H_{PMPC2-H}$); ^{13}C NMR (125 MHz) δ 13.9 (CH$_2$*C*H$_3$), 18.4 (CH(*C*H$_3$)$_2$), 20.0 (CH(*C*H$_3$)$_2$), 28.6 (*C*H(CH$_3$)$_2$), 53.9 (O=C*C*H), 55.4 (O*C*H$_3$), 62.7 (O*C*H$_2$CH$_3$), 64.0 (N*C*H), 82.4 (*C*HNO$_2$), 114.4 (*C*H$_{PMPC3}$), 125.9 (*C*H$_{PMPC2}$), 129.2 (*C*q$_{PMPC1}$), 158.5 (*C*q$_{PMPC4}$), 168.3 (O*C*=O), 170.6 (N*C*=O); *m/z* (EI$^+$) 350 (M$^+$, 100%), 303 (M$^+$-HNO$_2$, 16%), 231 (M$^+$-NO$_2$-CO$_2$Et,

64%), 188 (23%); HRMS found 350.14684, $C_{17}H_{22}N_2O_6$ requires 350.14724; Anal. Cald. For $C_{17}H_{22}N_2O_6$: C, 58.28, H, 6.33, N, 8.00. Found C, 57.92, H, 6.35, N, 7.82%.

((2*S, 3*S**, 4*R**)-4-ethyl-1-(4-methoxyphenyl)-3-nitropyrrolidin-2-yl)methanol 374**

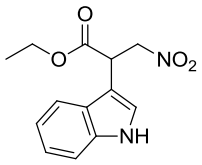


To a solution of pyrrolidinone **373** (43 mg, 0.14 mmol) in THF (2 mL) cooled to 0 ^oC was added a NaH (3 mg, 0.14 mmol) and the suspension stirred for 10 min. Then a solution of DIBAL (0.28 mL, 1 M in THF, 0.28 mmol) was added and the mixture warmed to 40 ^oC. The mixture was stirred at this temperature until complete consumption of the starting material (7 h). Water (10 mL) was then added and the mixture extracted with EtOAc (3x10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude pyrrolidine **374**. Purification by flash column chromatography (Petrol:EtOAc 8:2) gave pyrrolidine **374** (2 mg, 5%) as a colourless oil; R_f 0.57 (Petrol: EtOAc 8:2); IR υ_{max} (thin film) 3434 br (O-H), 2963 w (C-H), 2931 w (C-H), 1550 m (N=O), 1512 (C=C), 1463 w, 1360 w (N-O), 1243 m, 1181 w, 1038 w, 818 w cm^{-1}; ^1H NMR (600 MHz) δ 1.02 (3H, t, *J* = 7.5, C*H*$_3$), 1.61 (1H, m, C*H*$_2$CH$_3$), 1.61 (1H, br. s, O*H*), 1.78 (1H, m, C*H*$_2$CH$_3$), 2.82 (1H, m, C*H*Et), 3.30 (1H, dd, *J* = 7.5, 9.1, C*H*$_2$OH), 3.67 (1H, dd, *J* = 8.1, 9.1, C*H*$_2$OH), 3.77 (3H,s , OC*H*$_3$), 3.82 (1H, m, C*H*$_2$N), 3.92 (1H, dd, *J* = 4.5, 11.7, C*H*$_2$N), 4.30 (1H, ddd, *J* = 2.4, 4.8, 7.4, C*H*N), 4.99 (1H, dd, *J* = 5.4, 6.9, C*H*NO$_2$), 6.68 (2H, app d, *J* = 9.0, Arom. C*H*), 6.86 (2H, app d, *J* = 9.0, Arom. C*H*); ^{13}C NMR (125 MHz) δ 12.0 (*C*H$_3$), 25.2 (*C*H$_2$), 44.6 (*C*H), 55.7 (*C*H), 55.8 (*C*H$_2$), 60.1 (*C*H$_2$), 65.3 (*C*H), 91.3 (*C*H), 114.9 (*C*H Arom.), 115.6 (*C*H Arom.), 140.3 (*C*q Arom.), 152.9 (*C*q Arom.); *m/z* (EI$^+$) 280 (M$^+$, 15%), 203 (M$^+$-NO$_2$-CH$_2$OH, 75%), 174 (M+H$^+$-PMP, 68%), 84 (100%); HRMS found 280.14218, $C_{14}H_{20}N_2O_4$ requires 280.14176.

3.4.3 The 1,4-addition/nitro-Mannich reaction of non-zinc nucleophiles on *β*-nitrostyrene

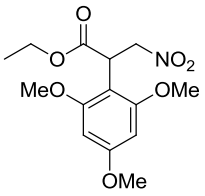
3.4.3.1 1,4-Additions to nitroacrylate

Ethyl 2-(1*H*-indol-3-yl)-3-nitropropanoate 381[180]



To a preformed mixture of $CeCl_3$·NaI·SiO_2 (11:2.5:1, 339 mg) was added MeCN (4 mL) followed by indole (69 mg, 0.59 mmol) and nitroacrylate **231** (85 mg, 0.59 mmol). The mixture was stirred for 30 min and then the solvent removed *in vacuo* and the residue stirred for 24 h. The mixture was then filtered through celite® with Et_2O (30 mL) and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **381** (140 mg, 89%) as a yellow oil; R_f 0.23 (Petrol:EtOAc 4:1); ^{1}H NMR (600 MHz) δ 1.24 (3H, t, *J* = 7.1, C*H*$_3$), 4.20 (2H, m, OC*H*$_2$), 4.65 (1H, dd, *J* = 14.5, 5.0, C*H*$_2$NO$_2$), 4.76 (1H, dd, *J* = 9.8, 4.9, C*H*CH$_2$), 5.22 (1H, dd, *J* = 14.4, 9.9, C*H*$_2$NO$_2$), 7.12 (1H, app d , *J* = 2.6, C*H* Arom.), 7.19 (1H, m, C*H* Arom.), 7.26 (1H, m, C*H* Arom.), 7.39 (1H, app d , *J* = 8.2, C*H* Arom.), 7.68 (1H, app d , *J* = 8.0, C*H* Arom.), 8.34 (1H, br s, N*H*), in agreement with that reported.[259]

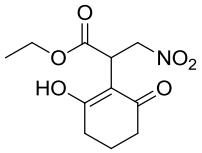
Ethyl 2-(2,4,6-trimethoxyphenyl)-3-nitropropanoate 382[180]



To a preformed mixture of $CeCl_3$·NaI·SiO_2 (11:2.5:1, 289 mg) was added MeCN (3 mL) followed by 1,3,5-trimethoxybenzene (84 mg, 0.50 mmol) and nitroacrylate **231** (73 mg, 0.50 mmol). The mixture was stirred for 30 min, the solvent removed *in vacuo* and the residue stirred for 24 h, then filtered through celite® with Et_2O (30 mL) and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:Et_2O

1:1) gave nitroalkane **382** (140 mg, 89%) as white crystals, mp. 107-108 °C; R_f 0.27 (Petrol:Et_2O 1:1); IR υ_{max} (thin film) 2952 w (C-H), 2843 w (C-H), 1732 s (C=O), 1609 s, 1594 s, 1554 s (N=O), 1500 m, 1459 m, 1420 m, 1378 m (N-O), 1344 w, 1329 w, 1226 m, 1203 s, 1152 s, 1119 s, 1058 w, 1029 m, 951 w, 815 m cm^{-1}; ^1H NMR (600 MHz) δ 1.18 (3H, t, *J* = 7.1, CH_2CH_3), 3.79 (6H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.10-4.21 (2H, m, OCH_2CH_3), 4.29 (1H, dd, *J* = 13.5, 5.2, CH_2NO_2), 5.05 (1H, dd, *J* = 8.8, 5.2, CHC=O), 5.12 (1H, dd, *J* = 13.5, 8.8, CH_2NO_2), 6.12 (2H, s, CH Arom.); ^{13}C NMR (150 MHz) δ 14.1 (CH_3), 38.0 (CHC=O), 55.3 (OCH_3), 55.7 (OCH_3), 61.1 (OCH_2CH_3), 74.3 (CH_2NO_2), 90.6 (CH Arom.), 103.8 (Cq Arom.), 158.6 (Cq Arom.), 161.3 (Cq Arom.), 171.6 (C=O); *m/z* (CI^+) 314 ($M+H^+$, 73%), 267 ($M+H^+-NO_2$, 100%), 240 (40%); HRMS: found 314.12450, $C_{14}H_{20}NO_7$ requires 314.12398.

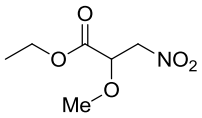
Ethyl 3-nitro-2-(2,6-dioxocyclohexyl)propanoate 384[183]



To a solution of 1,3-cyclohexadione (62 mg, 0.55 mmol) in MeOH (3 mL) was added triethylamine (77 μL, 0.55 mmol) at 0 °C, followed by a solution of nitroacrylate **231** (80 mg, 0.55 mmol) in MeOH (2 mL). The mixture was warmed to rt and stirred until complete consumption of the nitroacrylate (TLC, 2 h). A solution of HCl 0.5 M (10 mL) was then added and the mixture extracted with DCM (3x10 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:Me_2CO 1:1) gave nitroalkane **384** (140 mg, 99%) as a white solid, mp. 91-92 °C; R_f 0.47 (Petrol:Me_2CO 1:1); IR υ_{max} (thin film) 3420 w (O-H), 2981 w (C-H), 1710 s (C=O), 1584 s, 1557 s (N=O), 1382 s (N-O), 1282 m, 1248 m, 1192 m, 1031 m, 1012 m, 678 m cm^{-1}; ^1H NMR (600 MHz) δ 1.23 (3H, m, CH_3), 2.01 (2H, m, $CH_2CH_2CH_2$), 2.52 (4H, m, CH_2CH_2C=O), 4.16 (2H, m, CH_3CH_2O), 4.36 (1H, m, CH_2NO_2), 4.72 (1H, m, $CHCH_2NO_2$), 5.02 (1H, dd, *J* = 13.7, 8.4, CH_2NO_2), 8.62 (1H, br s, O-H); ^{13}C NMR (150 MHz) δ 13.9 (CH_2CH_3), 20.3 ($CH_2CH_2CH_2$), 32.5 (CH_2CH_2C=O), 37.5 ($CHCH_2NO_2$), 61.9 (OCH_2CH_3), 73.7 (CH_2NO_2), 110.1 (C=C-

OH), 171.8 (OC=O), 188.6 (CH_2C=O); *m/z* (CI^+) 178 ($M+H^+$, 30%), 211 (20%), 180 (27%), 165 (100%); HRMS: found 258.09712, $C_{11}H_{16}NO_6$ requires 258.09776.

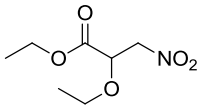
Ethyl 2-methoxy-3-nitropropanoate 389



A solution of nitroacrylate **231** (80 mg, 0.55 mmol) in methanol (5 mL) was stirred at reflux until complete consumption of the starting material (24 h). The solvent was then evaporated *in vacuo* and flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **389** (83 mg, 85%) as a colourless oil; R_f 0.44 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2984 w (C-H), 1937 w (C-H), 1751 s (C=O), 1736 s (C=O) 1557 s (N=O), 1379 m (N-O), 1193 s, 1129 s, 1038 m, 1017 m cm^{-1}; ^1H NMR (600 MHz) δ 1.31 (3H, t, *J* = 7.2, C*H*$_3$), 3.53 (3H, s, OC*H*$_3$), 4.27 (2H, m, OC*H*$_2$), 4.45 (1H, dd, *J* = 8.1, 3.5, C*H*OCH$_3$), 4.65 (1H, dd, *J* = 13.9, 8.2, C*H*$_2$NO$_2$), 4.72 (1H, dd, *J* = 13.9, 3.6, C*H*$_2$NO$_2$); ^{13}C NMR (150 MHz) δ 14.0 (CH_2CH_3), 59.5 (OCH$_3$), 62.1 (OC*H*$_2$), 75.8 (*C*H$_2$NO$_2$), 76.6 (*C*HOCH$_3$), 168.4 (*C*=O); *m/z* (EI^+) 178 (M^+, 100%); HRMS: found 178.07170, $C_6H_{11}NO_5$ requires 178.07155; Anal. Cald. For $C_6H_{11}NO_5$: C, 40.68, H, 6.26, N, 7.91. Found C, 40.38, H, 6.29, N, 7.57%.

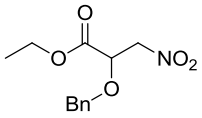
The product **389** was also isolated in low yield from the methylation of the respective nitroalcohol **255**.[187] A dry 50 mL round-bottom flask was charged with Proton-Sponge® (1.86 g, 8.68 mmol), $CHCl_3$ (16 mL) and methyl trifluoromethanesulfonate (880 μL, 7.81 mmol) at rt. The nitroalcohol **255** (283 mg, 1.74 mmol) was then added under stirring and the mixture stirred at reflux overnight (22 h). Then saturated aqueous NH_3 (3 mL) was added and the mixture stirred for 2 h at rt. Water (10 mL) was the added and the mixture extracted with DCM (2x20 mL), washed with 2 M HCl (10 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **289** (21 mg, 7%) as a colourless oil, identical to the one described above.

Ethyl 2-ethoxy-3-nitropropanoate 395



A solution of nitroacrylate **231** (100 mg, 0.69 mmol) in ethanol (7 mL) was stirred at reflux until complete consumption of the starting material (24 h). The solvent was then evaporated *in vacuo* and flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **395** (117 mg, 89%) as a colourless oil, R_f 0.33 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2923 w (C-H), 1753 m (C=O), 1736 m, 1559 s (N=O), 1379 m (N-O), 1200 m, 1130 m, 1052 m, 1019 m, 559 w m cm^{-1}; ^{1}H NMR (600 MHz) δ 1.21 (3H, t, *J* = 7.1, OCH_2CH_3), 1.31 (3H, t, *J* = 7.2, $O{=}COCH_2CH_3$), 3.56 (1H, m, OCH_2CH_3), 3.84 (1H, m, OCH_2CH_3), 4.26 (2H, m, $O{=}COCH_2CH_3$), 4.57 (1H, dd, *J* = 3.5, 8.4, O=C-C*H*-O), 4.64 (1H, dd, *J* = 8.5, 13.6, CH_2NO_2), 4.71 (1H, dd, *J* = 8.5, 13.5, CH_2NO_2); ^{13}C NMR (150 MHz) δ 14.1 ($O{=}COCH_2CH_3$), 14.9 ($CHOCH_2CH_3$), 62.0 ($O{=}COCH_2CH_3$), 67.7 ($CHOCH_2CH_3$), 75.1 (O=C-*C*H-O), 76.1 (CH_2NO_2), 168.8 (*C*=O); no M+ peak on mass spec; Anal. Cald. For $C_7H_{13}NO_5$: C, 43.98, H, 6.85, N, 7.33. Found C, 44.24, H, 6.86, N, 7.58%.

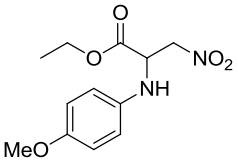
Ethyl 2-(benzyloxy)-3-nitropropanoate 396



A solution of nitroacrylate **231** (73 mg, 0.50 mmol) in benzyl alcohol (1 mL) was stirred at 100 ^oC until complete consumption of the starting material (24 h). The solvent was then evaporated *in vacuo* and flash column chromatography (Petrol:DCM 1:1) gave nitroalkane **396** (79 mg, 62%) as a colourless oil; R_f 0.46 (Petrol:DCM 1:1); IR υ_{max} (thin film) 2922 s (C-H), 2852 m (C-H), 1745 m (C=O), 1559 m (N=O), 1456 m, 1378 m (N-O), 1274 w, 1203 m, 1131 m, 1020 m cm^{-1}; ^{1}H NMR (600 MHz) δ 1.32 (3H, t, *J* = 7.1, CH_3), 4.28 (2H, m, OCH_2CH_3), 4.60 (1H, d, *J* = 11.2, CH_2Ph), 4.68 (3H, m, C*H*-O and CH_2NO_2), 4.87 (1H, d, *J* = 11.2, CH_2Ph), 7.30-7.38 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 14.1 (CH_3), 62.1 (OCH_2CH_3), 73.7 (CH_2Ph), 74.2 (*C*H-O), 76.0 (CH_2NO_2), 128.3 (*C*H Arom.), 128.4 (*C*H Arom.), 128.5 (*C*H Arom.),

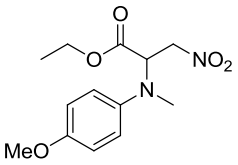
136.2 (*C*q Arom.), 168.6 (*C*=O); *m/z* (CI^+) 254 ($M+H^+$, 13%) (no HRMS), 181 ($M+H^+$-COOEt, 100%).

Ethyl 2-((4-methoxyphenyl)amino)-3-nitropropanoate 397



To a stirred solution of nitroacrylate **231** (201 mg, 1.39 mmol) in DCM (14 mL) was added at rt *para*-anisidine (307 mg, 2.50 mmol) and the mixture was stirred until complete consumption of the nitroacrylate (TLC, 1 h). The mixture was then evaporated and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **397** (364 mg, 98%) as an orange solid; mp. 74-75 ^oC, R_f 0.40 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 3387 s (N-H), 3010 w (C-H), 2956 w (C-H), 2917 w (C-H), 2836 w (C-H), 1732 s (C=O), 1546 s (N=O), 1515 s, 1317 m (N-O), 1250 m, 1233 m, 1210 s, 1186 m, 1152 m, 1031 m, 829 m, 806 m cm^{-1}; ^1H NMR (600 MHz) δ 1.29 (3H, t, *J* = 7.1, C*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 4.26 (1H, br. S, NH), 4.27 (2H, m, OC*H*$_2$), 4.55 (1H, t, *J* = 5.0, C*H*NH), 4.76 (1H, dd, *J* = 13.7, 4.8, C*H*$_2$NO$_2$), 4.82 (1H, dd, *J* = 13.7, 5.1, C*H*$_2$NO$_2$), 6.68 (2H, app d, *J* = 8.9, C*H*$_{PMPC3-H}$), 6.80 (2H, app d, *J* = 8.9, C*H*$_{PMPC2-H}$); ^{13}C NMR (150 MHz) δ 14.0 (CH$_2$*C*H$_3$), 55.6 (O*C*H$_3$), 56.3 (*C*HNH), 62.5 (O*C*H$_2$), 75.8 (*C*H$_2$NO$_2$), 114.9 (*C*H$_{PMPC3}$), 115.9 (*C*H$_{PMPC2}$), 139.2 (*C*q$_{PMPC1}$), 153.6 (*C*q$_{PMPC4}$), 169.7 (*C*=O); *m/z* (EI^+) 268 (M^+, 20%), 149 (100%), 134 (46%); HRMS: found 268.10592, $C_{12}H_{16}N_2O_5$ requires 268.10686; Anal. Cald. For $C_{12}H_{16}N_2O_5$: C, 53.73, H, 6.01, N, 10.44. Found C, 53.74, H, 6.00, N, 10.15%.

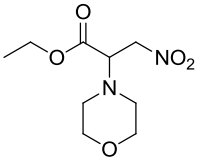
Ethyl 2-((4-methoxyphenyl)(methyl)amino)-3-nitropropanoate 406[260]



To a stirred solution of nitroalkane **397** (198 mg, 0.740 mmol) in THF (7 mL) was added at rt sodium borohydride (141 mg, 3.70 mmol) and paraformaldehyde (222 mg,

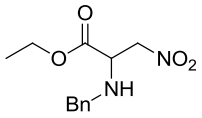
7.40 mmol). Trifluoroacetic acid (3.5 mL, 45 mmol) was then added dropwise over 1 h and the mixture stirred for another 1 h. A saturated aqueous solution of Na_2CO_3 was then added until pH = 11 and the mixture extracted with DCM (3x10 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **406** (78 mg, 37%) as an orange oil, R_f 0.48 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2961 w (C-H), 1730 s (C=O), 1557 s (N=O), 1513 s, 1247 m, 1035 m, 825 w cm^{-1}; ^1H NMR (600 MHz) δ 1.24 (3H, t, *J* = 6.7, CH_2CH_3), 2.82 (3H, s, NCH_3), 4.21 (2H, m, OCH_2), 4.77 (1H, dd, *J* = 13.4, 8.8, CH_2NO_2), 4.92 (1H, dd, *J* = 13.4, 6.0, CH_2NO_2), 5.06 (1H, dd, *J* = 8.7, 6.0, NC*H*), 6.86 (4H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 14.2 (CH_2CH_3), 35.0 (NCH_3), 55.6 (OCH_3), 61.9 (OCH_2), 63.2 (NC*H*), 73.6 (CH_2NO_2), 114.5 (CH_{PMPC3}), 117.9 (CH_{PMPC2}), 143.1 (Cq_{PMPC1}), 153.9 (Cq_{PMPC1}), 168.8 (*C*=O); *m/z* (EI^+) 282 (M^+, 31%), 163 (100%, M^+-NO_2-COOEt), 122 (25%); HRMS: found 282.12069, $C_{13}H_{18}N_2O_5$ requires 282.12102.

Ethyl 2-morpholino-3-nitropropanoate 398



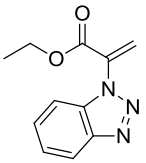
To a stirred solution of nitroacrylate **231** (80 mg, 0.55 mmol) in wet DCM (5 mL) was added at rt morpholine (54 μL, 0.66 mmol) and the mixture was stirred at rt until complete consumption of the nitroacrylate (TLC, 30 min). The mixture was then evaporated and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **398** (125 mg, 98%) as an orange oil, R_f 0.33 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2965 w (C-H), 2858 w (C-H), 1729 s (C=O), 1557 s (N=O), 1383 w (N-O), 1187 w, 1116 m, 1023 w, 855 w cm^{-1}; ^1H NMR (600 MHz) δ 1.31 (3H, t, *J* = 7.2, CH_3), 2.50 (2H, m, CH_2N), 2.80 (2H, m, CH_2N), 3.62 (4H, m, CH_2CH_2O), 4.03 (1H, dd, *J* = 8.9, 6.4, $CHCH_2$), 4.23 (2H, m, OCH_2CH_3), 4.61 (1H, dd, *J* = 13.5, 9.0, CH_2NO_2), 4.67 (1H, dd, *J* = 13.6, 6.4, CH_2NO_2); ^{13}C NMR (150 MHz) δ 14.3 (CH_2CH_3), 49.9 (CH_2N), 61.4 (OCH_2CH_3), 64.5 (*C*HN), 67.1 (CH_2CH_2O), 73.3 (CH_2NO_2), 168.1 (*C*=O); *m/z* (EI+) 232 (M^+, 7%), 159 (M^+-COOEt, 53%), 113 (M^+-NO_2-COOEt, 100%); HRMS: found 232.10474, $C_9H_{16}N_2O_5$ requires 232.10537.

Ethyl 2-(benzylamino)-3-nitropropanoate 399



To a stirred solution of nitroacrylate **231** (80 mg, 0.55 mmol) in DCM (5 mL) was added at 0 ^{o}C benzylamine (72 μL, 0.66 mmol) and the mixture was stirred at this temperature until complete consumption of the nitroacrylate (TLC, 1 h). The mixture was then evaporated and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **399** (112 mg, 81%) as an orange oil, R_f 0.59 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 3340 br (N-H), 3030 w (C-H), 2982 w (C-H), 2931 w (C-H), 1735 s (C=O), 1557 s (N=O), 1379 m (N-O), 1196 m, 1020 m, 739 m, 699 m cm^{-1}; ^{1}H NMR (600 MHz) δ 1.31 (3H, t, *J* = 7.1, C*H*$_3$), 2.27 (1H, br s, N*H*), 3.81 (1H, d, *J* = 13.3, C*H*$_2$NH), 3.85 (1H, dd, *J* = 6.1, 5.0, C*H*CH$_2$), 3.96 (1H, d, *J* = 13.3, C*H*$_2$NH), 4.26 (2H, m, OC*H*$_2$), 4.63 (1H, dd, *J* = 13.5, 4.9, C*H*$_2$NO$_2$), 4.67 (1H, dd, *J* = 13.5, 6.0, C*H*$_2$NO$_2$), 7.28 (1H, m , C*H* Arom.), 7.31-7.36 (4H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 14.0 (CH$_2$*C*H$_3$), 52.0 (*C*H$_2$NH), 57.7 (*C*HCH$_2$), 62.0 (O*C*H$_2$), 76.7 (*C*H$_2$NO$_2$), 127.4 (*C*H Arom.), 128.2 (*C*H Arom.), 128.5 (*C*H Arom.), 138.8 (*C*q Arom.), 170.8 (*C*=O); *m/z* (CI+) 253 (M+H$^+$, 4%), 179 (9%), 133 (M$^+$-NO$_2$-COOEt, 17%), 106 (PhCH=NH$_2^+$, 20%), 91 (PhCH$_3^+$, 100%); HRMS: found 253.11934, $C_{12}H_{17}N_2O_4$ requires 253.11883.

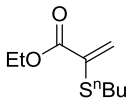
Ethyl 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)acrylate 402



To a solution of nitroacrylate **231** (72 mg, 0.50 mmol) in DCM (5 mL) was added 1*H*-benzo[d][1,2,3]triazole (65 mg, 0.55 mmol) and the mixture was stirred at rt until complete consumption of the nitroacrylate (TLC, 2 days). The mixture was then evaporated *in vacuo* to give crude acrylate **402**. Purification by flash column chromatography (Petrol:Et$_2$O 7:3) gave acrylate **402** (62 mg, 47%) as a colourless oil, R_f 0.38 (Petrol:Et$_2$O 7:3); IR υ_{max} (thin film) 2984 w (C-H), 1729 s (C=C), 1635 m, 1455 m, 1378 m, 1276 m, 1240 m, 1178 s, 1074 m, 1055 m, 1018 m, 785 m, 747 s

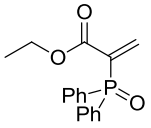
cm^{-1}; ^1H NMR (600 MHz) δ 1.32 (3H, t, *J* = 7.2, C*H*$_3$), 4.36 (2H, q, *J* = 7.2, OC*H*$_2$CH$_3$), 6.30 (1H, s, =C*H*$_2$), 6.74 (1H, s, =C*H*$_2$), 7.41 (1H, app. t, *J* = 7.8, C*H* Arom.), 7.44 (1H, app. d, *J* = 8.4, C*H* Arom.), 7.52 (1H, app. t, *J* = 7.4, C*H* Arom.), 8.10 (1H, d, *J* = 8.3, C*H* Arom.); ^{13}C NMR (150 MHz) δ 14.0 (*C*H$_3$), 62.5 (O*C*H$_2$CH$_3$), 110.6 (*C*H Arom.), 120.1 (*C*H Arom.), 124.2 (*C*H Arom.), 125.2 (=*C*H$_2$), 128.2 (*C*q Arom.), 133.1 (*C*q Arom.), 134.4 (=*C*-N), 145.8 (*C*q Arom.), 161.6 (*C*=O); *m/z* (CI^+) 218 ($M+H^+$, 100%), 161 (26%), 133 (98%); HRMS: found 218.09295, $C_{11}H_{12}N_3O_2$ requires 218.09247; Anal. Cald. For $C_{11}H_{11}N_3O_2$: C, 60.82, H, 5.10, N, 19.34. Found C, 60.53, H, 5.21, N, 19.63%.

Ethyl 2-(butylthio)acrylate 408[261]



To a stirred solution of nitroacrylate **231** (60 mg, 0.41 mmol) in THF (2 mL) was added at rt 1-butanethiol (180 μL, 1.24 mmol) and triethylamine (24 μL, 0.17 mmol) and the mixture was stirred overnight until complete consumption of the nitroalkene (TLC, 22 h). The mixture was then evaporated *in vacuo* and purification by flash column chromatography (Petrol: Et_2O 9:1) gave acrylate **408** (29 mg, 38%) as a colourless oil, which was found to be unstable and could not be completely characterised, R_f 0.38 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2959 m (C-H), 1719 s (C=C), 1583 m, 1465 m, 1385 m, 1277 m, 1248 s, 1117 s, 1025 m cm^{-1}; ^1H NMR (600 MHz) δ 1.33 (3H, m, C*H*$_3$), 1.47 (2H, m, CH$_2$C*H*$_2$CH$_3$), 1.66 (2H, m, C*H*$_2$CH$_2$CH$_3$), 2.72 (2H, m, SC*H*$_2$), 4.27 (2H, m, OC*H*$_2$CH$_3$), 5.40 (1H, s, =C*H*$_2$), 6.35 (1H, s, =C*H*$_2$); ^{13}C NMR (150 MHz) δ 13.6 (*C*H$_3$), 14.1 (OCH$_2$*C*H$_3$), 22.2 (CH$_2$C*H*$_2$CH$_3$), 29.7 (SCH$_2$C*H*$_2$), 31.1 (SC*H*$_2$), 61.7 (OC*H*$_2$), 118.5 (=*C*H$_2$), 137.9 (=*C*q), 164.6 (*C*=O); *m/z* (EI^+) 188 (M^+, 30%), 107 (100%); HRMS: found 188.08600, $C_9H_{16}O_2S$ requires 188.08655.

Ethyl 2-(diphenylphosphoryl)acrylate 409



To a stirred solution of the nitroacrylate **231** (65 mg, 0.45 mmol) in dry THF (5 mL), was added at rt diphenylphosphine oxide (100 mg, 0.500 mmol) and the mixture was stirred at rt overnight, until complete consumption of the nitroacrylate (TLC, 16 h). After completion, the mixture was evaporated and purification by flash column chromatography gave acrylate **409** (75 mg, 56%) as a yellow oil, R_f 0.29 (Petrol:Me_2CO 3:2); IR υ_{max} (thin film) 3058 w (C-H), 2981 w (C-H), 1721 s (C=O), 1438 s, 1250 m, 1184 s, 1118 s, 1098 s, 1019 m, 728 s, 695 s cm^{-1}; ^{1}H NMR (600 MHz) δ 1.05 (3H, t, *J* = 7.1, C*H*$_3$), 4.10 (2H, q, *J* = 7.1, OC*H*$_2$CH$_3$), 6.30 (1H, dd, $^{P\text{-}H}J$ = 17.4, ^2J = 1.4, =C*H*$_2$), 7.25 (1H, dd, $^{P\text{-}H}J$ = 33.6, ^2J = 1.4, =C*H*$_2$), 7.40-7.60 (6H, m, C*H* Arom.), 7.85 (4H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 13.7 (CH$_2$*C*H$_3$), 61.4 (O*C*H$_2$CH$_3$), 128.4 (d, *J* = 12.6, *C*H Arom.), 131.2 (d, *J* = 108.6, *C*q Arom.), 131.8 (d, *J* = 10.1, *C*H Arom.), 132.0 (d, *J* = 2.8, *C*H Arom.), 137.3 (d, *J* = 95.5, =*C*q-P), 144.6 (d, *J* = 4.9, =*C*H$_2$), 164.3 (d, *J* = 14.1, *C*=O); ^{31}P NMR (300 MHz) δ 26.0; *m/z* (ESI$^+$) 301 (M+H$^+$, 100%), 243 (55%), 215 (40%); HRMS: found 301.0996, $C_{17}H_{18}O_3P$ requires 301.0994.

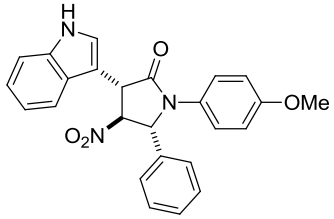
3.4.3.2 Nitro-Mannich reaction to nitroacrylate adducts

General procedure E for the synthesis of pyrrolidin-2-ones 232

A solution of nitroalkane (0.50 mmol) in THF (5 mL), was cooled to -78 °C and ^{n}BuLi (0.55 mmol, of a 2.5 M solution in hexanes, 1.1 equiv.) was added dropwise. The orange mixture was stirred at this temperature for 10 min before the corresponding imine (0.75 mmol, 1.5 equiv.) in THF (2 mL) was added *via* cannula. The mixture was stirred for 20 min, before TFA (1.00 mmol, 2.0 equiv.) in THF (0.5 mL) was added *via* cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt for 16 h. Saturated aqueous $NaHCO_3$ (20 mL) and Et_2O (20 mL) were then added and the layers separated. The aqueous phase was extracted with Et_2O (3x20 mL), and the combined organics washed with brine (20

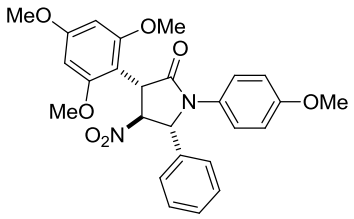
mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave crude pyrrolidinone. The pyrrolidinone was then purified further with column chromatography.

(3S*,4S*,5R*)-3-(1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one 420



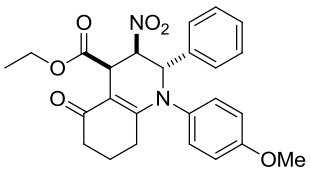
Prepared by general procedure E. Nitroalkane **381** (153 mg, 0.620 mmol), ^{n}BuLi (0.680 mmol), imine **281** (260 mg, 1.24 mmol) and TFA (1.54 mmol) afforded crude pyrrolidinone **420**. Purification by flash column chromatography (Petrol:EtOAc 3:2) gave pyrrolidinone **420** (141 mg, 54%, 79% based on recovered starting material) as an orange solid; mp. 196-197 °C; R_f 0.34 (Petrol:EtOAc 3:2); IR υ_{max} (thin film) 3329 br (N-H), 2960 w (C-H), 1701 s (C=O), 1555 s (N=O), 1512 s, 1364 m (N-O), 1250 m, 743 m cm^{-1}; ^{1}H NMR (600 MHz) δ 3.74 (1H, s, OC*H*$_3$), 4.92 (1H, d, *J* = 7.9, C*H*PhN), 5.27 (1H, dd, *J* = 7.8, 6.5, C*H*NO_2), 5.73 (1H, d, *J* = 6.3, C*H*C=O), 6.85 (3H, m, C*H* Arom.), 7.21 (2H, m, C*H* Arom.), 7.23-7.36 (7H, m, C*H* Arom.), 7.64 (1H, m, C*H* Arom.), 8.70 (1H, br s, N*H*); ^{13}C NMR (150 MHz) δ 46.5 (*C*HC=O), 55.3 (O*C*H_3), 65.9 (*C*HPhN), 92.4 (*C*HNO_2), 108.5 (*C*q Arom.), 112.0 (*C*H Arom.), 114.2 (*C*H Arom.), 118.1 (*C*H Arom.), 120.2 (*C*H Arom.), 122.5 (*C*H Arom.), 124.3 (*C*H Arom.), 125.4 (*C*H Arom.), 125.4 (*C*q Arom.), 126.9 (*C*H Arom.), 129.2 (*C*H Arom.), 129.2 (*C*q Arom.), 129.3 (*C*H Arom.), 136.2 (*C*q Arom.), 136.6 (*C*q Arom.), 157.7 (*C*q Arom.), 170.8 (*C*=O); *m/z* (EI^+) 427 (M^+, 20%), 380 (100%, M^+-HNO_2), 351 ($M+H^+$-Ph, 17%), 230 (10%), 210 (17%); HRMS: found 427.15312, $C_{18}H_{20}N_3O_4$ requires 427.15266.

(3*S,4*S**,5*R**)-1-(4-methoxyphenyl)-4-nitro-5-phenyl-3-(2,4,6-trimethoxyphenyl)pyrrolidin-2-one 421**



Prepared by general procedure E. Nitroalkane **382** (126 mg, 0.400 mmol), ^{n}BuLi (0.40 mmol), imine **281** (170 mg, 0.800 mmol) and TFA (1.40 mmol) afforded crude pyrrolidinone **421**. Purification by flash column chromatography (Petrol:Me_2CO 7:3) gave pyrrolidinone **421** (102 mg, 53%) as a white solid; mp. 96-97 °C; R_f 0.28 (Petrol:Me_2CO 7:3); IR υ_{max} (thin film) 3003 w (C-H), 2940 w (C-H), 2839 w (C-H), 1713 s (C=O), 1611 s, 1595 s, 1553 s (N=O), 1512 s, 1457 m, 1364 m (N-O), 1249 s, 1205 s, 1152 s, 1118 s, 1033 m, 835 m, 817 m, 701 m cm^{-1}; ^{1}H NMR (600 MHz) δ 3.72 (3H, s, OC*H*$_3$), 3.77 (3H, br. s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 3.95 (3H, br. s, OC*H*$_3$), 5.12 (1H, d, *J* = 9.5, C*H*C=O), 5.26 (1H, dd, *J* = 9.6, 7.5, C*H*NO_2), 5.70 (1H, d, *J* = 7.5, PhC*H*N), 6.18 (2H, m, C*H* Arom.), 6.78 (2H, app. d, *J* = 9.1, C$H_{PMPC3\text{-}H}$), 7.24 (1H, app. d, *J* = 9.1, C$H_{PMPC2\text{-}H}$), 7.26-7.32 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 44.2 (*C*HC=O), 55.3, 55.4, 55.8 and 56.0 (O*C*H_3), 65.0 (Ph*C*HN), 90.9 and 91.4 (*C*H Arom.), 92.2 (*C*HNO_2), 104.1 (*C*q Arom.), 114.0 (*C*H Arom.), 125.0 (*C*H Arom.), 127.1 (*C*H Arom.), 128.9 (*C*H Arom.), 129.0 (*C*H Arom.), 129.7 (*C*q Arom.), 137.4 (*C*q Arom.), 157.1 (*C*q Arom.), 158.6 (*C*q Arom.), 159.7 (*C*q Arom.), 161.6 (*C*q Arom.), 170.0 (*C*=O); *m/z* (EI$^+$) 479 (M+H$^+$, 100%), 432 (M+H$^+$-NO_2, 70%), 264 (30%); HRMS: found 479.1808, $C_{18}H_{20}N_3O_4$ requires 479.1818; Anal. Cald. For $C_{26}H_{27}N_2O_7$: C, 65.26, H, 5.48, N, 5.85. Found C, 65.39, H, 5.78, N, 5.59%.

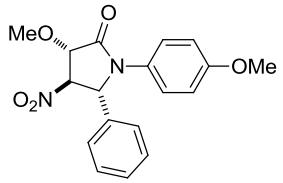
(2*S,3*R**,4*R**)-Ethyl 1-(4-methoxyphenyl)-3-nitro-5-oxo-2-phenyl-1,2,3,4,5,6,7,8-octahydroquinoline-4-carboxylate 422**



Prepared by general procedure E. Nitroalkane **384** (36 mg, 0.14 mmol), ^{n}BuLi (0.28 mmol), imine **281** (59 mg, 0.28 mmol) and TFA (0.49 mmol) afforded crude

quinoline **422**. Purification by flash column chromatography (Petrol:Me_2CO 7:3) gave quinoline **422** (24 mg, 38%) as a yellow oil; R_f 0.17 (Petrol:Me_2CO 7:3); IR υ_{max} (thin film) 2932 w (C-H), 1730 m (C=O), 1557 s (N=O), 1508 s, 1396 m, 1247 s, 1181 s, 1027 m, 841 m, 733 m, 702 m cm^{-1}; ^1H NMR (600 MHz) δ 1.28 (3H, t, *J* = 7.2, CH_2CH_3), 1.92 (2H, m, $CH_2CH_2CH_2$), 2.22 (2H, m, CH_2CH_2C=), 2.40 (2H, m, CH_2C=O), 3.74 (3H, s, OCH_3), 4.22 (2H, m, CH_3CH_2O), 4.43 (1H, d, *J* = 5.3, CHCOOEt), 5.19 (1H, dd, *J* = 8.7, 5.3, $CHNO_2$), 5.24 (1H, d, *J* = 8.8, CHPh), 6.40-6.90 (4H, br, CH Arom.), 7.15 (2H, m, CH Arom.), 7.26 (3H, m, CH Arom.); ^{13}C NMR (150 MHz) δ 14.0 (CH_2CH_3), 21.3 ($CH_2CH_2CH_2$), 28.9 (CH_2CH_2C=), 35.8 (CH_2C=O), 39.6 (CHCOOEt), 55.3 (OCH_3), 61.8 (OCH_2CH_3), 63.7 (CHPh), 85.5 ($CHNO_2$), 104.2 (C=CC=O), 114.6 (CH_{PMPC3} at 60°C), 128.2 (CH Arom.), 28.9 (CH Arom.), 129.1 (CH Arom.), 130.1 (CH Arom., at 60°C), 134.7 (Cq Arom.), 135.3 (Cq Arom.), 158.9 (Cq_{PMPC4}), 161.3 (Cq Arom.), 171.0 (OC=O), 193.8 (CH_2C=O); *m/z* (EI^+) 450 (M^+, 32%), 404 (M^+-NO_2, 86%), 330 (M^+-HNO_2-COOEt, 100%), 254 (M^+-NO_2-COOEt -Ph, 35%); HRMS: found 450.17902, $C_{25}H_{26}N_2O_6$ requires 450.17854.

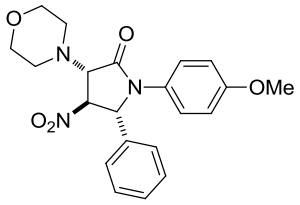
(3S*,4R*,5R*)-3-methoxy-1-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one 423



Prepared by general procedure E. Nitroalkane **389** (75 mg, 0.42 mmol), ^{n}BuLi (0.460 mmol), imine **281** (134 mg, 0.640 mmol) and TFA (0.850 mmol) afforded crude pyrrolidinone **423**. Purification by flash column chromatography (Petrol:EtOAc 7:3) gave pyrrolidinone **423** (60 mg, 42%) as an orange oil that was unstable (degradation was observed after 30 min at rt); R_f 0.35 (Petrol:EtOAc 7:3); IR υ_{max} (thin film) 2958 w (C-H), 2925 w (C-H), 1713 s (C=O), 1555 s (N=O), 1511 s, 1367 m (N-O), 1248 m, 1106 m, 1030 m, 834 m, 700 m cm^{-1}; ^1H NMR (600 MHz) δ 3.72 (1H, s, OCH_3), 3.75 (1H, s, OCH_3), 4.74 (1H, d, *J* = 6.0, CHOMe), 5.02 (1H, t, *J* = 5.8, $CHNO_2$), 5.48 (1H, d, *J* = 5.7, CHN), 6.78 (2H, app d, *J* = 9.1, $CH_{PMPC3\text{-}H}$), 7.20 (2H, app d, *J* = 9.1, $CH_{PMPC2\text{-}H}$), 7.21-7.40 (5H, m, CH Arom.); ^{13}C NMR (150 MHz) δ 55.3 (OCH_3), 59.6 (OCH_3), 64.1 (CHPhN), 81.2 (CHOMe), 91.1 ($CHNO_2$), 114.2 (CH_{PMPC3}), 125.3

(*C*H Arom.), 127.1 (*C*H Arom.), 128.4 (*C*q Arom.), 129.3 (*C*H Arom.), 129.4 (*C*H Arom.), 135.9 (*C*q Arom.), 157.9 (Cq_{PMPC4}), 167.2 (*C*=O); *m/z* (EI^+) 342 (M^+, 100%), 266 (23%, M^+-Ph+H), 147 (17%); HRMS: found 342.12084, $C_{18}H_{18}N_2O_5$ requires 342.12102.

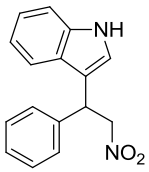
(3S*,4R*,5R*)-1-(4-methoxyphenyl)-3-morpholino-4-nitro-5-phenylpyrrolidin-2-one 424



Prepared by general procedure E. Nitroalkane **398** (105 mg, 0.450 mmol), ^{n}BuLi (0.500 mmol), imine **281** (143 mg, 0.680 mmol) and TFA (0.990 mmol) afforded crude pyrrolidinone **424**. Purification by flash column chromatography (Petrol:EtOAc 3:2) gave pyrrolidinone **424** (118 mg, 50%) as an orange oil that was unstable (degradation was observed after 30 min at rt); R_f 0.31 (Petrol:EtOAc 3:2); IR υ_{max} (thin film) 2961 w (C-H), 2853 w (C-H), 1709 m (C=O), 1557 m (N=O), 1512 s, 1249 s, 1115 m, 1031 w, 835 w cm^{-1}; ^{1}H NMR (600 MHz) δ 2.87 (4H, m, NC*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 3.78 (4H, m, OC*H*$_2$), 4.46 (1H, d, *J* = 7.4, CHC=O), 5.10 (1H, dd, *J* = 7.4, 6.2, C*H*NO_2), 5.50 (1H, d, *J* = 6.2, C*H*PhN), 6.79 (2H, app d, C*H* Arom.), 7.15-7.35 (7H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 49.3 (N*C*H$_2$), 55.3 (O*C*H$_3$), 64.2 (*C*HPhN), 66.8 (O*C*H$_2$), 70.4 (N*C*HC=O), 87.3 (*C*HNO_2), 114.2 ($CH_{PMPC3\text{-}H}$), 125.0 (*C*H Arom.), 126.6 (*C*H Arom.), 128.8 (*C*q Arom.), 129.3 (*C*H Arom.), 129.4 (*C*H Arom.), 136.4 (*C*q Arom.), 157.7 (*C*q Arom.), 167.0 (*C*=O); *m/z* (CI^+) 398 ($M+H^+$, 7%), 310 (M^+-C_4H_5NO, 11%), 266 ($M+H^+$- C_4H_5NO-NO_2, 18%), 227 (72%), 105 (100%); HRMS: found 398.17131, $C_{21}H_{24}N_3O_5$ requires 398.17160.

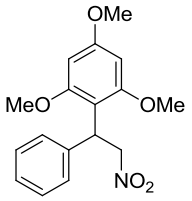
3.4.3.3 1,4-Additions to *β*-nitrostyrene

3-(2-nitro-1-phenylethyl)-1*H*-indole 429[180]



To a preformed mixture of $CeCl_3 \cdot NaI \cdot SiO_2$ (11:2.5:1, 289 mg) was added MeCN (3 mL) followed by indole (59 mg, 0.50 mmol) and *β*-nitrostyrene (74 mg, 0.50 mmol). The mixture was stirred for 30 min, the solvent removed *in vacuo* and the residue stirred for 24 h. The mixture was then filtered through celite® with Et_2O (30 mL) and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **429** (123 mg, 92%) as a colourless oil, R_f 0.43 (Petrol:EtOAc 4:1); ^{1}H NMR (600 MHz) δ 4.96 (1H, dd, *J* = 12.4, 8.4, C*H*$_2$NO$_2$), 5.09 (1H, dd, *J* = 12.4, 7.7, C*H*$_2$NO$_2$), 5.21 (1H, t, *J* = 8.1, C*H*), 7.04 (1H, d, *J* = 2.3, C*H* Arom.), 7.10 (1H, app. t, *J* = 7.5, C*H* Arom.), 7.22 (1H, app. t, *J* = 7.5, C*H* Arom.), 7.29 (1H, m, C*H* Arom.), 7.35 (5H, m, C*H* Arom.), 7.47 (1H, d, *J* = 7.9, C*H* Arom.), 8.09 (1H, br. s, N*H*); ^{13}C NMR (150 MHz) δ 41.5 (*C*HCH$_2$), 79.5 (*C*H$_2$), 111.4 (*C*H$_{indoleC8}$), 114.4 (*C*q$_{indoleC3}$), 118.9 (*C*H Arom.), 119.9 (*C*H Arom.), 121.6 (*C*H Arom.), 122.7 (*C*H Arom.), 126.0 (*C*q Arom.), 127.5 (*C*H Arom.), 127.7 (*C*H Arom.), 128.9 (*C*H Arom.), 136.4 (*C*q Arom.), 139.1 (*C*q Arom.). Data in agreement with that reported.[262]

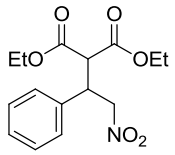
1,3,5-Trimethoxy-2-(2-nitro-1-phenylethyl)benzene 430[180]



To a preformed mixture of $CeCl_3 \cdot NaI \cdot SiO_2$ (11:2.5:1, 289 mg) was added MeCN (3 mL) followed by 1,3,5-trimethoxybenzene (84 mg, 0.50 mmol) and *β*-nitrostyrene (74 mg, 0.50 mmol). The mixture was stirred for 30 min, the solvent removed *in vacuo* and the residue stirred for 24 h. The mixture was then filtered through celite® with Et_2O (30 mL) and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **430** (113 mg, 71%) as a colourless oil, R_f 0.43

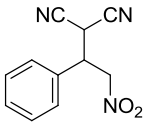
(Petrol:EtOAc 4:1); ^{1}H NMR (600 MHz) δ 3.80 (3H, s, OCH_3), 3.81 (6H, s, OCH_3), 5.14 (1H, dd, *J* = 12.8, 7.6, CH_2NO_2), 5.26 (1H, dd, *J* = 12.7, 8.1, CH_2NO_2), 5.51 (1H, t, *J* = 7.9, C*H*), 6.14 (2H, s, C$H_{trimethoxybenzene}$), 7.19 (1H, t, *J* = 7.3, C*H* Arom.), 7.27 (2H, t, *J* = 7.4, C*H* Arom.), 7.33 (2H, d, *J* = 7.6, C*H* Arom.); ^{13}C NMR (150 MHz) δ 38.5 (*C*HCH_2), 55.2 (O*C*H_3), 55.7 (O*C*H_3), 78.3 (*C*H_2), 91.0 (*C*$H_{trimethoxybenzene}$), 108.5 (*C*q Arom.), 126.5 (*C*H Arom.), 127.5 (*C*H Arom.), 128.2 (*C*H Arom.), 140.4 (*C*$q_{trimethoxybenzene}$), 158.9 (*C*q-OMe), 160.5 (*C*q-OMe). Data in agreement with that reported.[263]

Diethyl 2-(2-nitro-1-phenylethyl)malonate 431[182]



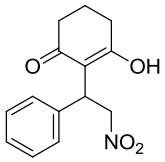
To a solution of diethylmalonate (0.15 mL, 1.0 mmol) in THF (3 mL) was added NaH (24 mg, 1.0 mmol, 95%) and the mixture stirred at rt for 15 min. A solution of *β*-nitrostyrene (74 mg, 0.50 mmol) in THF (2 mL) was then added and the mixture stirred at rt until complete consumption of the nitroalkene (TLC, 15 min). The mixture was then quenched with addition of saturated aqueous NH_4Cl (10 mL) and extracted with DCM (3x10 mL), the combined organics then washed with brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude nitroalkane **431**. Purification by flash column chromatography (Hexane:Et_2O 7:3) gave nitroalkane **431** (148 mg, 96%) as a colourless oil; R_f 0.30 (Hexane:Et_2O 7:3); ^{1}H NMR (600 MHz) δ 1.05 (3H, t, *J* = 7.1, CH_3), 1.27 (3H, t, *J* = 7.1, CH_3), 3.83 (1H, d, *J* = 9.4, C*H*C=O), 4.02 (2H, q, *J* = 7.2, O*C*H_2), 4.27 (3H, m, O*C*H_2 and PhC*H*), 4.85 (1H, dd, *J* = 13.1, 9.4, CH_2NO_2), 4.95 (1H, dd, *J* = 13.1, 4.8, CH_2NO_2), 7.23-7.34 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 13.7 (*C*H_3), 14.0 (*C*H_3), 42.9 (*C*HPh), 54.9 (O=C*C*HC=O), 61.9 (O*C*H_2), 62.2 (O*C*H_2), 77.6 (*C*H_2NO_2), 128.0 (*C*H Arom.), 128.4 (*C*H Arom.), 128.9 (*C*H Arom.), 136.1 (*C*q Arom.), 166.8 (*C*=O), 167.5 (*C*=O). Data in agreement with that reported.[264]

2-(2-Nitro-1-phenylethyl)malononitrile 432[181]



To a solution of L-Proline (11.5 mg, 10 mol %) in DMF (1 mL) was added malononitrile (66 mg, 1.0 mmol) followed by *β*-nitrostyrene (149 mg, 1.00 mmol) and the mixture was stirred at rt until complete consumption of the nitroalkene (TLC, 20 h). Water (10 mL) was then added and the mixture was extracted with Et_2O (3x10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude nitroalkane **432**. Purification by flash column chromatography (DCM) gave nitroalkane **432** (192 mg, 89%) as a yellow oil; R_f 0.49 (DCM); ^{1}H NMR (600 MHz) δ 4.09 (1H, m, PhC*H*), 4.43 (1H, d, *J* = 6.0, NCC*H*CN), 4.90 (1H, dd, *J* = 14.2, 6.2, CH_2NO$_2$), 4.97 (1H, dd, *J* = 14.3, 7.9, CH_2NO$_2$), 7.30-7.48 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 27.6 (Ph*C*H), 43.7 (NC*C*HCN), 74.9 (*C*H_2NO$_2$), 110.3 (C≡N), 110.4 (C≡N), 127.7 (*C*H Arom.), 129.9 (*C*H Arom.), 130.4 (*C*H Arom.), 131.8 (*C*q Arom.). Data in agreement with that reported.[181]

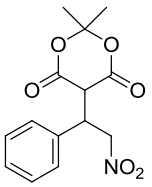
3-Hydroxy-2-(2-nitro-1-phenylethyl)cyclohex-2-enone 433[183]



To a solution of 1,3-cyclohexanedione (560 mg, 5.00 mmol) in methanol (1 mL) was added a solution of sodium (25 mg, 1.1 mmol) in methanol (2 mL) and the mixture stirred for 1 min at rt. The mixture was then cooled to 0 ^{o}C, a solution of *β*-nitrostyrene (745 mg, 5.00 mmol) in methanol (2 mL) was added and the mixture stirred at this temperature for 30 min, then at rt until complete consumption of the starting material (TLC, 5 h). The mixture was poured into ice-water, neutralised with 10% HCl, filtered and recrystallised from methanol to give pure nitroalkane **433** (440 mg, 34%, lit. 68%) as a white solid; mp. 142-143 ^{o}C (lit. 144-146 ^{o}C); R_f 0.35 (Petrol:Me_2CO 1:1); ^{1}H NMR (600 MHz) δ 1.86 (2H, m, CH_2), 2.37 (4H, m, CH_2), 5.08 (2H, m, CH_2NO$_2$), 5.19 (1H, m, C*H*Ph), 7.19-7.34 (5H, m, C*H* Arom.), 9.91 (1H,

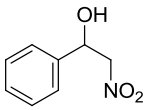
br. s, O*H*); ^{13}C NMR (150 MHz) δ 20.4 (*C*H$_2$), 33.0 (*C*H$_2$), 35.2 (*C*H$_2$), 38.2 (*C*HPh), 77.3 (*C*H$_2$NO$_2$), 114.4 (*C*q), 126.9 (*C*H Arom.), 127.8 (*C*H Arom.), 128.4 (*C*H Arom.), 138.8 (*C*q Arom.), 139.7 (HO-*C*q), 197.4 (*C*=O). Data in agreement with that reported.[265]

2,2-Dimethyl-5-(2-nitro-1-phenylethyl)-1,3-dioxane-4,6-dione 434[197]



To a solution of Meldrum's acid (144 mg, 1.00 mmol) in DCM (7 mL) was added triethylamine (130 μL, 1.00 mmol) and the mixture stirred at rt for 30 min. *β*-nitrostyrene (149 mg, 1.00 mmol) was then added in one batch and the mixture stirred at rt until complete consumption of the starting material (TLC, 1 h). The mixture was acidified to pH = 2 with addition of 10% HCl, extracted with DCM (3x10 mL), dried over MgSO$_4$ and evaporated *in vacuo* to give pure nitroalkane **434** (280 mg, 96%, lit. 88%) as a white solid; mp. 92-94 ^{o}C (lit. 93-95 ^{o}C); R$_f$ 0.49 (DCM:MeOH 10:1); ^{1}H NMR (600 MHz) δ 1.39 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 4.04 (1H, d, *J* = 3.2, O=CC*H*C=O), 4.64 (1H, m, C*H*Ph), 5.02 (1H, dd, *J* = 14.0, 6.5, C*H*$_2$NO$_2$), 5.40 (1H, dd, *J* = 14.0, 9.0, C*H*$_2$NO$_2$), 7.30-7.35 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 27.6 (*C*H$_3$), 28.1 (*C*H$_3$), 41.8 (O=C*C*HC=O), 48.5 (*C*HPh), 75.9 (*C*H$_2$NO$_2$), 105.9 (*C*q), 128.8 (*C*H Arom.), 128.9 (*C*H Arom.), 129.2 (*C*H Arom.), 135.1 (*C*q Arom.), 164.0 (*C*=O), 164.4 (*C*=O). Data in agreement with that reported.[197]

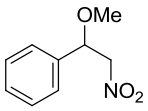
2-Nitro-1-phenylethanol 435[115]



In a 5 mL round bottom flask were added benzaldehyde (300 μL, 3.00 mmol), nitromethane (810 μL, 15.0 mmol) and triethylamine (1.46 mL, 10.5 mmol) and the

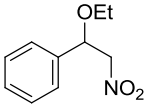
mixture stirred at rt overnight (20 h), then evaporated *in vacuo* to give crude nitroalcohol **435**. Purification by flash column chromatography (Petrol:Et_2O 4:1) gave nitroalcohol **435** (247 mg, 50%) as a colourless oil; R_f 0.17 (Petrol:Et_2O 4:1); ^1H NMR (600 MHz) δ 2.90 (1H, br. s, O*H*), 4.52 (1H, dd, *J* = 13.3, 2.7, CH_2NO_2), 4.61 (1H, dd, *J* = 13.1, 9.6, CH_2NO_2), 5.47 (1H, d, *J* = 10.0, C*H*OH), 7.35-7.45 (5H, m, C*H* Arom.). Data in agreement with that reported.[266]

(1-Methoxy-2-nitroethyl)benzene 436



A 1.5 M solution of MeONa in MeOH (670 μL, 1.00 mmol) was added at rt to a solution of *β*-nitrostyrene (149 mg, 1.00 mmol) in MeOH (10 mL). The mixture was stirred at rt until no nitroalkene was observed on TLC (15 min). Acetic acid (400 μL, 6.00 mmol) was then added and the mixture stirred for 5 min and then poured into water (20 mL). The mixture was extracted with DCM (3x10 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude nitroalkane **436**. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **436** (133 mg, 73%, lit. 60%[198]) as a colourless oil, R_f 0.63 (Petrol:Et_2O 9:1); ^1H NMR (600 MHz) δ 3.28 (3H, s, OCH_3), 4.41 (1H, dd, *J* = 12.8, 3.3, CH_2NO_2), 4.62 (1H, dd, *J* = 12.7, 10.1, CH_2NO_2), 4.97 (1H, dd, *J* = 10.2, 3.4, C*H*OCH_3), 7.36-7.45 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 57.1 (*C*H_3), 80.0 (*C*H), 80.4 (*C*H_2), 126.8 (*C*H Arom.), 129.0 (*C*H Arom.), 129.1 (*C*H Arom.), 135.9 (*C*q Arom.). Data in agreement with that reported.[198]

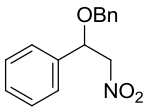
(1-Ethoxy-2-nitroethyl)benzene 438



A 1.5 M solution of EtONa in EtOH (670 μL, 1.00 mmol) was added at rt to a solution of *β*-nitrostyrene (149 mg, 1.00 mmol) in EtOH (10 mL). The mixture was

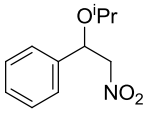
stirred at rt until no nitroalkene was observed on TLC (15 min). Acetic acid (400 µL, 6.00 mmol) was then added and the mixture stirred for 5 min and then poured into water (20 mL). The mixture was extracted with DCM (3x10 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude nitroalkane **438**. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **438** (129 mg, 66%, lit. 6%[198]) as a colourless oil; R_f 0.49 (Petrol:Et_2O 9:1); ^{1}H NMR (600 MHz) δ 1.16 (3H, t, *J* = 7.3, C*H*$_3$), 3.39 (2H, m, OC*H*$_2$), 4.39 (1H, dd, *J* = 12.8, 3.4, C*H*$_2$NO$_2$), 4.61 (1H, dd, *J* = 12.8, 10.3, C*H*$_2$NO$_2$), 5.06 (1H, dd, *J* = 10.0, 3.3, C*H*O), 7.35-7.42 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 14.9 (*C*H$_3$), 62.9 (O*C*H$_2$), 78.2 (*C*H), 80.5 (*C*H$_2$NO$_2$), 126.7 (*C*H Arom.), 128.9 (*C*H Arom.), 129.0 (*C*H Arom.), 136.7 (*C*q Arom.). Data in agreement with that reported.[198]

(1-(Benzyloxy)-2-nitroethyl)benzene 439



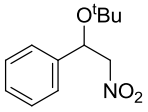
A 1.5 M solution of BnONa in BnOH (670 µL, 1.00 mmol) was added at rt to a solution of *β*-nitrostyrene (149 mg, 1.00 mmol) in BnOH (10 mL). The mixture was stirred at rt until no nitroalkene was observed on TLC (15 min). Acetic acid (400 µL, 6.00 mmol) was added and the mixture stirred for 5 min and then poured into water (20 mL). The mixture was extracted with DCM (3x10 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude nitroalkane **439**. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **439** (171 mg, 66%, lit. 30%[198]) as a colourless oil; R_f 0.39 (Petrol:Et_2O 9:1); ^{1}H NMR (600 MHz) δ 4.34 (1H, d, *J* = 11.6, OC*H*$_2$), 4.42 (1H, dd, *J* = 12.8, 3.4, C*H*$_2$NO$_2$), 4.52 (1H, d, *J* = 11.5, OC*H*$_2$), 4.70 (1H, dd, *J* = 12.8, 10.1, C*H*$_2$NO$_2$), 5.16 (1H, dd, *J* = 10.2, 3.4, C*H*O), 7.23-7.41 (9H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 70.9 (O*C*H$_2$), 77.5 (*C*H), 80.3 (*C*H$_2$NO$_2$), 127.0 (*C*H Arom.), 127.9 (*C*H Arom.), 128.0 (*C*H Arom.), 128.4 (*C*H Arom.), 129.2 (*C*H Arom.), 129.2 (*C*H Arom.), 136.0 (*C*q Arom.), 136.9 (*C*q Arom.). Data in agreement with that reported.[198]

(1-Isopropoxy-2-nitroethyl)benzene 440



A 0.5 M solution of ^{i}PrONa in ^{i}PrOH (2.00 mL, 1.00 mmol) was added at rt to a solution of *β*-nitrostyrene (149 mg, 1.00 mmol) in ^{i}PrOH (8 mL). The mixture was stirred at rt until no nitroalkene was observed on TLC (10 min). Acetic acid (400 μL, 6.00 mmol) was then added and the mixture stirred for 5 min and then poured into water (20 mL). The mixture was extracted with DCM (3x10 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude nitroalkane **440**. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **440** (121 mg, 58%) as a colourless oil; R_f 0.51 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2974 w (C-H), 1553 s (N=O), 1494 w, 1454 w, 1418 w, 1379 m (N-O), 1336 w, 1224 w, 1143 w, 1122 w, 1095 m, 1062 m, 1029 w, 976 m, 762 m, 717 m, 699 s cm^{-1}; ^{1}H NMR (600 MHz) δ 1.07 (3H, d, *J* = 6.2, C*H*$_3$), 1.13 (3H, d, *J* = 6.2, C*H*$_3$), 3.56 (1H, sept, *J* = 6.1, C*H*(CH$_3$)$_2$), 4.36 (1H, dd, *J* = 12.7, 3.3, C*H*$_2$NO$_2$), 4.57 (1H, dd, *J* = 12.6, 10.3, C*H*$_2$NO$_2$), 5.17 (1H, dd, *J* = 10.2, 3.2, C*H*OCH), 7.35 (1H, m, C*H* Arom.), 7.40 (4H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 20.8 (*C*H$_3$), 23.2 (*C*H$_3$), 70.4 (*C*H(CH$_3$)$_2$), 75.8 (O*C*HCH$_2$), 80.8 (*C*H$_2$NO$_2$), 126.7 (*C*H Arom.), 128.8 (*C*H Arom.), 128.9 (*C*H Arom.), 137.5 (*C*q Arom.); *m/z* (CI$^+$) 210 (M+H$^+$, 6%), 162 (M$^+$-HNO$_2$, 24%), 149 (M$^+$-CH$_2$NO$_2$, 61%), 107 (PhCHO+H$^+$, 100%), 104 (PhCH=CH$_2^+$, 72%); HRMS: found 210.11276, $C_{11}H_{16}NO_3$ requires 210.11302.

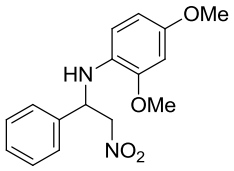
(1-(*tert*-Butoxy)-2-nitroethyl)benzene 441



A 0.53 M solution of ^{t}BuONa in ^{t}BuOH (1.90 mL, 1.00 mmol) was added at rt to a solution of *β*-nitrostyrene (149 mg, 1.00 mmol) in THF (10 mL) and the mixture turned yellow instantly. The mixture was stirred at this temperature for 5 min and then acetic acid (4.00 μL, 6.00 mmol) was added, the mixture stirred for 5 min and then poured into water (20 mL). The mixture was extracted with DCM (3x10 mL), the combined organics washed with brine (10 mL), dried over $MgSO_4$ and evaporated *in*

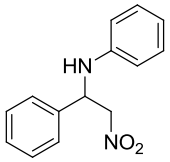
vacuo to give crude nitroalkane **441**. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **441** (89 mg, 40%) as a white solid, mp. 45-46 ^oC; R_f 0.57 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2977 w (C-H), 1555 s (N=O), 1455 w, 1379 m (N-O), 1190 m, 1092 m, 1066 m, 963 m, 765 w, 722 w, 701 m cm^{-1}; ^1H NMR (600 MHz) δ 1.10 (9H, s, CH_3), 4.32 (1H, dd, J = 12.0, 3.3, CH_2NO_2), 4.49 (1H, dd, J = 12.0, 10.2, CH_2NO_2), 5.27 (1H, dd, J = 10.1, 3.2, OC*H*), 7.31-7.41 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 28.3 (*C*H_3), 72.0 (O*C*H), 75.5 (*C*q), 81.9 (*C*H_2NO_2), 126.2 (*C*H Arom.), 128.3 (*C*H Arom.), 128.7 (*C*H Arom.), 140.2 (*C*q Arom.); *m/z* (CI^+) 224 ($M+H^+$, 6%), 163 ($M+H^+$-CH_3NO_2, 65%), 150 ($M+H^+$-*t*BuOH, 26%), 107 (PhCHO+H^+, 100%); HRMS: found 224.12912, $C_{12}H_{18}NO_3$ requires 224.12867; Anal. Cald. For $C_{12}H_{17}NO_3$: C, 64.55, H, 7.67, N, 6.27. Found C, 64.76, H, 7.79, N, 6.07%.

2,4-Dimethoxy-*N*-(2-nitro-1-phenylethyl)aniline 442



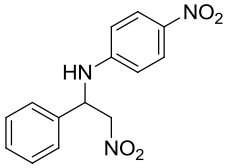
To a solution of *β*-nitrostyrene (149 mg, 1.00 mmol) in dry DCM (5 mL) was added 2,3-dimethoxyaniline (184 mg, 1.20 mmol) at rt and the mixture was stirred overnight until no more nitroalkene was observed (TLC, 19 h). The mixture was then evaporated *in vacuo* and purification by flash column chromatography (Petrol:EtOAc 4:1) gave the aniline **442** (212 mg, 70%) as a yellow oil; R_f 0.38 (Petrol:EtOAc 4:1); ^1H NMR (600 MHz) δ 3.72 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.66 (1H, br. s, N*H*), 4.70 (1H, dd, J = 12.3, 5.5, CH_2NO_2), 4.73 (1H, dd, J = 12.2, 8.3, CH_2NO_2), 5.13 (1H, dd, J = 8.0, 5.9, PhC*H*), 6.31 (1H, dd, J = 8.8, 2.6, C*H* Arom.), 6.45 (2H, d, J = 2.5, C*H* Arom.), 7.32 (1H, m, C*H* Arom.), 7.39 (4H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 55.6 (O*C*H_3), 55.6 (O*C*H_3), 57.2 (O*C*H_3), 80.1 (*C*H_2), 99.2 (*C*HCH_2), 103.5 (*C*H Arom.), 111.9 (*C*H Arom.), 126.5 (*C*H Arom.), 128.5 (*C*H Arom.), 129.2 (*C*H Arom.), 129.6 (*C*q Arom.), 138.1 (*C*q Arom.), 148.3 (*C*q Arom.), 152.8 (*C*q Arom.). Data in agreement with that reported.[60]

_N_-(2-Nitro-1-phenylethyl)aniline 443[199]



In a 10 mL round-bottom flask was added *β*-nitrostyrene (149 mg, 1.00 mmol), aniline (110 μL, 1.20 mmol) and H_2O (4 mL) and the mixture was stirred vigorously for 2 h. The mixture was then extracted with DCM (3x10 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **443** (163 mg, 67%) as a yellow oil, R_f 0.28 (Petrol:Et_2O 9:1); ^{1}H NMR (600 MHz) δ 4.44 (1H, d, *J* = 6.6, N*H*), 4.73 (2H, d, *J* = 6.7, CH_2), 5.21 (1H, q, *J* = 6.9, C*H*), 6.65 (2H, d, *J* = 8.0, C*H* Arom.), 6.78 (1H, t, *J* = 7.4, C*H* Arom.), 7.18 (2H, t, *J* = 7.9, C*H* Arom.), 7.36 (1H, m, C*H* Arom.), 7.42 (4H, m , C*H* Arom.); ^{13}C NMR (150 MHz) δ 56.5 (*C*H), 79.9 (*C*H_2), 113.8 (*C*H Arom.), 118.8 (*C*H Arom.), 126.4 (*C*H Arom.), 128.6 (*C*H Arom.), 129.2 (*C*H Arom.), 129.3 (*C*H Arom.), 137.6 (*C*q Arom.), 145.6 (*C*q Arom.). Data in agreement to that reported.[267]

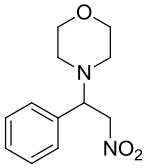
4-Nitro-_N_-(2-nitro-1-phenylethyl)aniline 444



To a solution of *para*-nitroaniline (138 mg, 1.00 mmol) in dry THF (10 mL) cooled at -78 ^{o}C, was added ^{n}BuLi (400 μL, 2.5 M in hexane, 1.00 mmol) and the mixture stirred for 10 min, before a solution of *β*-nitrostyrene (149 mg, 1.00 mmol) in dry THF (2 mL) was added dropwise. The mixture was stirred at this temperature for 10 min and then let to warm to rt and stirred until complete consumption of the starting nitroalkene (TLC, 1.5 h). Saturated aqueous $NaHCO_3$ solution (10 mL) was then added and the mixture extracted with DCM (3x10 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **444** (129 mg, 45%) as a yellow oil; R_f 0.21 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 3365 br (N-H), 3065 w (C-H), 2922 w (C-H), 1596 s (C=C), 1551 s (N=O), 1503 m, 1476 m, 1378 w (N-O), 1302 s, 1277 s, 1184 m, 1110 s, 833 m, 752 m, 698 s cm^{-1}; ^{1}H NMR (600 MHz) δ 4.79 (2H, m, CH_2NO$_2$), 5.28 (1H, m, C*H*NH),

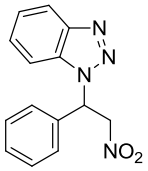
5.40 (1H, d, *J* = 6.5, N*H*), 6.59 (2H, app. d, *J* = 8.9, C$H_{anilineC1\text{-}H}$), 7.36-7.44 (5H, m, C*H* Arom.), 8.05 (2H, app. d, *J* = 8.9, C$H_{anilineC2\text{-}H}$); ^{13}C NMR (150 MHz) δ 56.0 (C*H*N), 79.6 (*C*H_2NO_2), 112.5 (*C*$H_{anilineC2}$), 126.2 (*C*$H_{anilineC3}$), 126.2 (*C*H Arom.), 129.2 (*C*H Arom.), 129.2 (*C*H Arom.), 129.6 (*C*H Arom.), 135.9 (*C*$q_{anilineC4}$), 139.3 (*C*q Arom.), 151.0 (*C*$q_{anilineC1}$); *m/z* (EI$^+$) 287 (M^+, 25%), 227 (85%), 181 (17%), 138 (24%), 104 (100%); HRMS: found 287.09031, $C_{14}H_{13}N_3O_4$ requires 287.09005.

_N_-(2-Nitro-1-phenylethyl)morpholine 445[200]



To a solution of *β*-nitrostyrene (149 mg, 1.00 mmol) in DCM (5 mL) was added morpholine (87 μL, 1.0 mmol) followed by $Sm(OTf)_3$ (1 mg, 0.2 mol%) and the mixture was stirred at rt overnight until the nitroalkene was consumed (TLC, 24 h). DCM (10 mL) was then added, the mixture washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give nitroalkane **445** (222 mg, 94%) as a red oil, used without further purification; R_f 0.46 (Petrol:EtOAc 4:1); ^{1}H NMR (600 MHz) δ 2.36 (2H, m, NCH_2), 2.52 (2H, m, NCH_2), 3.64 (4H, m, OCH_2), 4.34 (1H, dd, *J* = 9.5, 5.8, C*H*), 4.57 (1H, dd, *J* = 12.3, 5.8, CH_2NO_2), 4.99 (1H, dd, *J* = 12.3, 9.5, CH_2NO_2), 7.20 (2H, m, C*H* Arom.), 7.37 (3H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 49.8 (N*C*H_2), 66.9 (O*C*H_2), 66.9 (*C*H), 79.6 (*C*H_2NO_2), 128.3 (*C*H Arom.), 128.6 (*C*H Arom.), 129.3 (*C*H Arom.), 133.6 (*C*q Arom.). Data in agreement to that reported.[200]

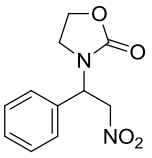
1-(2-nitro-1-phenylethyl)-1*H*-benzo[*d*][1,2,3]triazole 446[201]



To a solution of *β*-nitrostyrene **380** (74 mg, 0.50 mmol) in DCM (5 mL) was added 1*H*-benzo[d][1,2,3]triazole (65 mg, 0.55 mmol) followed by Et_3N (6 μL, 10 mol%)

and the mixture was stirred at rt until complete consumption of the nitroalkene (TLC, 19 h). The mixture was then evaporated *in vacuo* to give crude nitroalkane **446**. Purification by flash column chromatography (Petrol:Et_2O 7:3) gave nitroalkane **446** (111 mg, 83%) as a colourless oil, R_f 0.45 (Petrol:Et_2O 7:3); ^{1}H NMR (600 MHz) δ 5.16 (1H, dd, *J* = 14.8, 4.8, C$H_2$$NO_2$), 5.95 (1H, dd, *J* = 14.6, 9.8, C$H_2$$NO_2$), 6.60 (1H, dd, *J* = 9.8, 4.8, C*H*N), 7.36 (2H, m, C*H* Arom.), 7.43 (3H, m, C*H* Arom.), 8.07 (1H, d, *J* = 8.4, C*H* Arom.); ^{13}C NMR (150 MHz) δ 59.7 (*C*HN), 76.5 (C$H_2$$NO_2$), 109.3 (*C*H Arom.), 120.1 (*C*H Arom.), 124.5 (*C*H Arom.), 126.8 (*C*H Arom.), 128.0 (*C*H Arom.), 129.5 (*C*H Arom.), 129.7 (*C*H Arom.), 132.6 (*C*$q_{triazole}$), 133.9 (*C*$q_{triazole}$), 146.1 (*C*q Arom.). Data in agreement with that reported.[268]

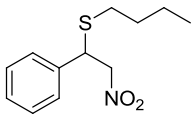
3-(2-Nitro-1-phenylethyl)oxazolidin-2-one 447[190]



To a mixture of 2-oxazolidinone (87 mg, 1 mmol), ^{t}BuOK (112 mg, 1 mmol) and 18-crown-6 (264 mg, 1.00 mmol) was added dry THF (5 mL) and the mixture was stirred at rt for 1 h. The mixture was then cooled to -78 ^{o}C and a solution of *β*-nitrostyrene (149 mg, 1.00 mmol) in THF (5 mL) was added and the mixture stirred at this temperature until complete consumption of the starting material (TLC, 30 min). A saturated aqueous solution of NH_4Cl (20 mL) was then added and the mixture warmed to rt and extracted with Et_2O (3x20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:Me_2CO 7:3) gave nitroalkane **447** (213 mg, 90%) as a colourless oil, R_f 0.50 (Petrol:Me_2CO 3:2); IR υ_{max} (thin film) 2976 w (C-H), 2925 w (C-H), 1740 s (C=O), 1553 s (N=O), 1482 w, 1419 m, 1380 m (N-O), 1248 m, 1111 w, 1076 w, 1047 m, 761 m, 733 s, 699 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.36 (1H, dt, *J* = 8.0, 8.8, NCH_2), 3.61(1H, m, NCH_2), 4.29 (2H, m, OCH_2), 4.86 (1H, dd, *J* = 5.4, 13.0, C$H_2$$NO_2$), 5.28 (1H, dd, *J* = 10.3, 13.0, C$H_2$$NO_2$), 5.58 (1H, dd, *J* = 5.4, 10.3, C*H*N), 7.31-7.35 (2H, m, C*H* Arom.), 7.37-7.43 (3H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 42.0 (*C*H_2N), 55.7 (*C*HN), 62.2 (O*C*H_2), 74.5 (*C*$H_2$$NO_2$), 127.3 (*C*H Arom.), 129.3 (*C*H Arom.), 133.6 (*C*q Arom.), 157.6 (*C*=O), one *C*H peak missing; *m/z* (CI$^+$) 237 (M+H$^+$, 100%), 176 (M$^+$-CH_3NO_2,

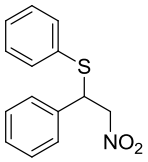
67%); HRMS: found 237.08724, $C_{11}H_{13}N_2O_4$ requires 237.08753; Anal. Cald. For $C_{11}H_{12}N_2O_4$: C, 55.93, H, 5.12, N, 11.86. Found C, 56.19, H, 5.23, N, 11.60%.

Butyl(2-nitro-1-phenylethyl)sulfane 448[261]



To a stirred solution of *β*-nitrostyrene (74 mg, 0.50 mmol) in ethanol (1 mL) was added 1-butanethiol (53 μL, 0.50 mmol) at rt followed by Et_3N (4 μL, 5 mol%) when the mixture was instantly decolorized and after 5 min of stirring the mixture was evaporated to give pure nitroalkane **448** (114 mg, 95%) as a colourless oil, used without further purification; R_f 0.63 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2959 w (C-H), 2930 w, 2873 w. 1555 (N=O), 1455 w, 1376 m (N-O), 747 w, 699 m cm^{-1}; ^1H NMR (600 MHz) δ 0.87 (3H, t, *J* = 7.4, C*H*$_3$), 1.35 (2H, m, C*H*$_2$CH$_3$), 1.53 (2H, qui., *J* = 7.6, C*H*$_2$), 2.45 (2H, t, *J* = 7.4, SC*H*$_2$), 4.56 (1H, t, *J* = 7.9, SC*H*), 4.76 (2H, d, *J* = 7.8, C*H*$_2$NO$_2$), 7.30-7.38 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 13.5 (*C*H$_3$), 21.8 (*C*H$_2$CH$_3$), 31.1 (*C*H$_2$), 31.3 (*C*H$_2$), 46.5 (*C*HS), 79.3 (*C*H$_2$NO$_2$), 127.6 (*C*H Arom.), 128.4 (*C*H Arom.), 129.0 (*C*H Arom.), 137.4 (*C*q Arom.); *m/z* (CI^+) 240 ($M+H^+$, 100%), 193 (M^+-NO_2, 56%), 179 (69%), 150 (M^+-BuS, 67%); HRMS: found 240.10582, $C_{12}H_{18}NO_2S$ requires 240.10617; Anal. Cald. For $C_{12}H_{17}NO_2S$: C, 60.22, H, 7.16, N, 5.85. Found C, 60.32, H, 7.21, N, 5.92%.

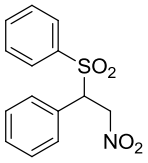
(2-Nitro-1-phenylethyl)(phenyl)sulfane 449[261]



To a stirred solution of *β*-nitrostyrene (74 mg, 0.50 mmol) in ethanol (2 mL) was added thiophenol (51 μL, 0.50 mmol) at rt, followed by Et_3N (4 μL, 5 mol%). The mixture was instantly decolourised and after 5 min of stirring the mixture was evaporated to give pure nitroalkane **449** (125 mg, 97%) as a colourless oil, used without further purification; R_f 0.67 (Petrol:Et_2O 9:1); ^1H NMR (600 MHz) δ 4.73

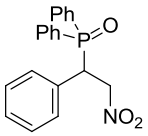
(1H, dd, *J* = 12.8, 6.0, SC*H*), 4.86 (1H, m, CH_2NO_2), 4.91 (1H, m, CH_2NO_2), 7.27-7.44 (10H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 49.7 (S*C*H), 78.4 (*C*H_2), 127.6 (*C*H Arom.), 128.5 (*C*H Arom.), 128.7 (*C*H Arom.), 128.9 (*C*H Arom.), 129.3 (*C*H Arom.), 131.7 (*C*q Arom.), 133.7 (*C*H Arom.), 136.2 (*C*q Arom.). Data in agreement with that reported.[269]

(2-Nitro-1-(phenylsulfonyl)ethyl)benzene 451[270]



To a solution of thioether **449** (259 mg, 1.00 mmol) in MeOH (5 mL), cooled to 0 ^{o}C, was added Oxone® (923 mg, 1.50 mmol) in H_2O (10 mL) and the resulting suspension was stirred for 1 h, then left to warm to rt and stirred overnight (22 h). After completion H_2O (10 mL) was added and the mixture extracted with DCM (3x10 mL). The combined organics were then washed with brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give pure sulfone **451** (301 mg, 97%) as a white solid used without further purification, mp. 180-181 ^{o}C; R_f 0.49 (Petrol:Et_2O 4:1); IR υ_{max} (thin film) 3068 w (C-H), 3009 w (C-H), 2956 w (C-H), 1553 s (N=O), 1496 w, 1447 m, 1417 m, 1374 m (N-O), 1360 w, 1298 s, 1280 m, 1143 s, 1080 m, 852 w, 760 m, 727 s, 700 s, 688 s cm^{-1}; ^{1}H NMR (600 MHz) δ 4.99 (1H, dd, *J* = 10.1, 4.7, C*H*SO_2), 5.10 (1H, dd, *J* = 14.0, 10.0, CH_2NO_2), 5.37 (1H, dd, *J* = 14.0, 4.6, CH_2NO_2), 7.14 (2H, m, C*H* Arom.), 7.29 (2H, m, C*H* Arom.), 7.36 (1H, m, C*H* Arom.), 7.45 (2H, m, C*H* Arom.), 7.55 (2H, m, C*H* Arom.), 7.63 (1H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 67.9 (*C*HSO_2), 72.7 (*C*H_2NO_2), 128.7 (*C*q Arom.), 129.0 (*C*H Arom.), 129.1 (*C*H Arom.), 129.1 (*C*H Arom.), 129.4 (*C*H Arom.), 130.0 (*C*H Arom.), 134.5 (*C*H Arom.), 135.8 (*C*q Arom.); *m/z* (CI^+) 292 (M^+, 30%), 251 (11%), 186 (13%), 150 (100%); HRMS: found 292.06466, $C_{14}H_{13}NO_4S$ requires 292.06435; Anal. Cald. For $C_{14}H_{13}NO_4S$: C, 57.72, H, 4.50, N, 4.81. Found C, 57.71, H, 4.40, N, 4.72%.

(2-Nitro-1-phenylethyl)diphenylphosphine oxide 450[271]



To a solution of *β*-nitrostyrene **380** (74 mg, 0.50 mmol) in THF (2 mL) at rt was added diphenylphosphine oxide (101 mg, 0.50 mmol) followed by Et_3N (4 μL, 5 mol %) and the mixture was stirred at rt until the nitroalkene was consumed (TLC, 24 h). After completion, the mixture was evaporated to give crude phosphine oxide **450**. Purification by flash column chromatography (Petrol:Me_2CO 1:1) gave phosphine oxide **450** (157 mg, 89%, lit. 86%) as a white solid, mp. 206-207 °C (lit. 208-209 °C); R_f 0.61 (Petrol:Me_2CO 1:1); ^{1}H NMR (600 MHz) δ 4.42 (1H, m, C*H*), 4.76 (1H, m, CH_2NO_2), 5.12 (1H, m, CH_2NO_2), 7.21-7.28 (7H, m, C*H* Arom.), 7.39-7.44 (3H, m, C*H* Arom.), 7.62 (3H, m, C*H* Arom.), 7.99 (2H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 45.8 (d, *J* = 64.0, *C*H), 72.7 (d, *J* = 5.9, *C*H_2NO_2), 128.2 (d, *J* = 2.5, *C*H Arom.), 128.3 (d, *J* = 12.3, *C*H Arom.), 128.7 (d, *J* = 1.7, *C*H Arom.), 129.3 (d, *J* = 11.6, *C*H Arom.), 129.4 (d, *J* = 5.1, *C*H Arom.), 129.6 (d, *J* = 8.6, *C*q Arom.), 130.3 (*C*q Arom.), 130.9 (d, *J* = 9.2, *C*H Arom.), 131.1 (d, *J* = 8.8, *C*H Arom.), 131.6 (d, *J* = 5.6, *C*q Arom.), 132.0 (d, *J* = 2.8, *C*H Arom.), 132.7 (d, *J* = 2.8, *C*H Arom.). Data in agreement to that reported.[271]

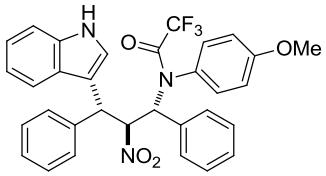
3.4.3.4 Nitro-Mannich reaction to *β*-nitrostyrene adducts

General procedure F for the synthesis of *β*-nitroamides 452

A solution of nitroalkane (0.500 mmol) in THF (5 mL), was cooled to -78 °C and ^{n}BuLi (0.550 mmol, of a 2.5 M solution in hexanes, 1.1 equiv.) was added dropwise. The orange mixture was stirred at this temperature for 10 min, before the corresponding imine (1.00 mmol, 2.0 equiv.) in THF (2 mL) was added *via* cannula. The mixture was stirred for 10 min before a 1:1 vol. mixture of TFA:THF (TFA 1.75 mmol, 3.5 equiv.) was added dropwise. The mixture was stirred at this temperature for a further 1 h, then warmed to rt over 5 min and quenched with saturated aqueous $NaHCO_3$ (10 mL) extracted with Et_2O (3x10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give crude *β*-nitroamine. A sample was taken for ^{1}H NMR

analysis and the rest of the crude product was dissolved in DCM (6 mL), cooled to -78 °C and then pyridine (140 µL, 1.50 mmol) and trifluoroacetic anhydride (240 µL, 1.50 mmol) were added. The mixture was then warmed to rt and stirred for a further 3 h. The mixture was then washed with aqueous HCl 2 M (3x10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave crude trifluoroacetamide, which was purified further with flash column chromatography.

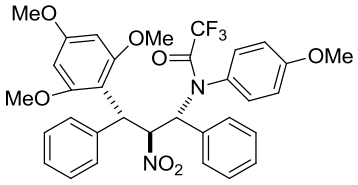
_N_-((1_R_*,2_S_*,3_R_*)-3-(1_H_-indol-3-yl)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide 455



Prepared by general procedure F. Nitroalkane **429** (123 mg, 0.460 mmol), ^{n}BuLi (184 µL, 2.5 M, 0.460 mmol), imine **281** (194 mg, 0.920 mmol) and TFA (123 µL, 1.61 mmol) afforded after TFA-protection crude trifluoroacetamide **455**. Purification by flash column chromatography (Petrol:Et_2O 1:1) gave trifluoroacetamide **455** (133 mg, 50%) as a colourless oil; R_f 0.34 (Petrol:Et_2O 1:1); IR υ_{max} (thin film) 3420 w (N-H), 3063 w, 3034 w, 2927 w, 2840 w (C-H), 1691 s (C=O), 1606 w, 1555 s (N=O), 1510 w, 1497 m, 1456 m, 1414 w, 1367 w (N-O), 1301 w, 1255 m, 1206 s, 1180 s, 1157 s, 1112 w, 1033 m, 840 m, 756 m, 734 s, 699 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.74 (3H, s, OC*H*$_3$), 4.91 (1H, d, *J* = 6.7, PhC*H*Cq), 5.92 (1H, dd, *J* = 8.9, 2.8, C*H* Arom.), 6.25 (1H, d, *J* = 9.2, C*H*NC=O), 6.40 (1H, dd, *J* = 6.6, 9.2, C*H*NO_2), 6.49 (1H, dd, *J* = 8.8, 3.0, C*H* Arom.), 6.63 (1H, dd, *J* = 8.8, 3.0, C*H* Arom.), 6.79 (1H, dd, *J* = 8.7, 2.7, C*H* Arom.), 6.92 (2H, dd, *J* = 8.2, 1.1, C*H* Arom.), 7.01-7.34 (9H, m, C*H* Arom.), 7.41 (3H, m, C*H* Arom.), 6.92 (1H, d, *J* = 2.5, C*H* Arom.), 8.25 (1H, br. s, N*H*); ^{13}C NMR (150 MHz) δ 43.9 (Ph*C*H), 55.3 (O*C*H_3), 62.8 (*C*HNC=O), 89.1 (*C*HNO_2), 111.2 (*C*H Arom.), 113.4 (*C*H Arom.), 113.6 (*C*H Arom.), 114.7 (*C*q Arom.), 116.1 (q, *J* = 289.0, *C*F_3), 118.8, 120.0, 122.3, 122.6, 127.7, 128.4, 128.6, 128.7, 129.3, 129.6, 131.1 and 132.5 (*C*H Arom.), 126.4, 126.9, 132.8, 136.0 and 138.3 (*C*q Arom), 158.3 (q, J = 35.5, *C*=O), 160.1 (*C*q Arom); ^{19}F NMR (282 MHz) δ -67.60 (3F, s, C*F*$_3$); *m/z*

(EI$^+$) 573 (M$^+$, 27%), 308 (M$^+$-NO_2-PMP-NH-TFA, 100%), 206 (PhCH$^+$-(Indole), 32%); HRMS: found 573.18730, $C_{32}H_{26}F_3N_3O_4$ requires 573.18699.

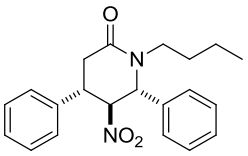
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R,2*S**,3*R**)-2-nitro-1,3-diphenyl-3-(2,4,6-trimethoxyphenyl)propyl)acetamide 456**



Prepared by general procedure F. Nitroalkane **430** (113 mg, 0.360 mmol), ^{n}BuLi (144 µL, 2.5 M, 0.360 mmol), imine **281** (150 mg, 0.720 mmol) and TFA (96 µL, 1.26 mmol) afforded after TFA-protection crude trifluoroacetamide **456**. Purification by flash column chromatography (Petrol:Et_2O 4:1) gave trifluoroacetamide **456** (185 mg, 83%) as a white solid, mp. 185-186 ^oC; R_f 0.13 (Petrol:Et_2O 4:1); IR υ_{max} (thin film) 3031 w (C-H), 2939 w (C-H), 2841 w (C-H), 1696 s (C=O), 1605 s, 1590 s, 1550 s (N=O), 1510 s, 1495 m, 1455 s, 1418 w, 1365 w (N-O), 1254 w, 1203 s, 1180 s, 1150 s, 1122 s, 1059 m, 1035 m, 952 w, 814 m, 735 s, 699 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.30 (3H, br. s, OC*H*$_3$), 3.72 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 4.05 (3H, br. s, OC*H*$_3$), 5.14 (1H, d, *J* = 11.5, PhC*H*Ar), 5.70-6.20 (2H, br. s, C*H* Arom.), 5.78 (1H, d, *J* = 6.8, C*H*NC=O), 6.01 (1H, dd, *J* = 9.0, 2.9, C*H* Arom.), 6.35 (1H, dd, *J* = 9.0, 3.1, C*H* Arom.), 6.73 (2H, d, *J* = 7.6, C*H* Arom.), 6.76 (1H, dd, *J* = 8.8, 2.9, C*H* Arom.), 7.01 (2H, app. t, *J* = 7.6, C*H* Arom.), 7.04 (1H, m, C*H* Arom.), 7.13 (1H, dd, *J* = 11.5, 6.8, C*H*NO_2), 7.15-7.19 (4H, m, C*H* Arom.), 7.46 (2H, app. d, *J* = 7.6, C*H* Arom.); ^{13}C NMR (150 MHz) δ 41.2 (PhCHCHNO_2), 55.3 (O*C*H_3), 65.2 (*C*HNC=O), 87.0 (*C*HNO_2), 90.0 (*C*H Arom.), 107.3 (*C*q Arom.), 112.9 (*C*H Arom.), 113.4 (*C*H Arom.), 116.1 (*C*F_3, q, *J* = 288.7), 126.7 and 127.4 (*C*H Arom.), 127.7 (*C*q Arom.), 127.9, 128.2, 128.3 and 131.6 (*C*H Arom.), 131.6 (*C*q Arom.), 131.7 and 132.7 (*C*H Arom.), 140.1 (*C*q Arom.), 157.5 (O=*C*CF_3, q, *J* = 35.6), 159.5 and 160.6 (*C*q Arom.); ^{19}F NMR (282 MHz) δ -67.74 (3F, s, C*F*$_3$); *m/z* (ES$^+$) 647 (M+Na$^+$, 20%), 625 (M+H$^+$, 15%), 578 (M$^+$-NO_2, 15%), 457 (25%), 378 (15%), 359 (M$^+$-NO_2-PMP-NH-TFA, 70%), 257 ((OMe)$_3C_6H_3CH^+$Ph, 100%); HRMS: found 647.2003,

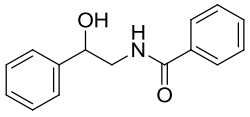
$C_{33}H_{31}F_3N_2O_7Na$ requires 647.1981; Anal. Cald. For $C_{22}H_{26}N_2O_5$: C, 63.46, H, 5.00, N, 4.48. Found C, 63.36, H, 4.96, N, 4.44%.

(4*S,5*S**,6*R**)-1-butyl-5-nitro-4,6-diphenylpiperidin-2-one 462**[195]



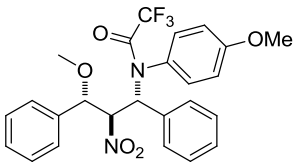
In a 10 mL round bottom flask were added nitroalkane **433** (147 mg, 0.50 mmol), benzoic acid (92 mg, 0.75 mmol) and toluene (3 mL). Nitrogen was bubbled through the mixture for 10 min and then ^{n}butyl amine (74 μL, 0.75 mmol) and benzaldehyde (76 μL, 0.75 mmol) were added. The reaction was heated to 70 ^{o}C in a sealed vessel and monitored by TLC. After 20 h the mixture was evaporated *in vacuo* and dissolved in DCM (20 mL), then washed with aqueous HCl 2 M (3x10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave piperidinone **462** (50 mg, 28%) as a white solid; mp. 210-211 ^{o}C; R_f 0.29 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2984 w (C-H), 1729 s (C=C), 1635 m, 1455 m, 1378 m (N-O), 1276 m, 1240 m, 1178 s, 1074 m, 1055 m, 1018 m, 785 m, 747 s cm^{-1}; ^{1}H NMR (600 MHz) δ 0.86 (3H, t, *J* = 7.4, C*H*$_3$), 1.24 (2H, m, C*H*$_2$CH$_3$), 1.50 (2H, m, CH$_2$C*H*$_2$CH$_2$), 2.54 (1H, m, NC*H*$_2$), 2.82 (1H, dd, *J* = 13.2, 17.4, O=CC*H*$_2$), 2.90 (1H, dd, *J* = 4.8, 17.4, O=CC*H*$_2$), 3.73 (1H, ddd, *J* = 13.2, 11.3, 4.8, CH$_2$C*H*Ph), 3.96 (1H, ddd, *J* = 13.7, 9.7, 6.4, NC*H*$_2$), 4.99 (1H, dd, *J* = 8.5, 11.3, C*H*NO$_2$), 5.05 (1H, d, *J* = 8.6, NC*H*Ph), 7.17-7.40 (10H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 13.7 (*C*H$_3$), 20.0 (*C*H$_2$CH$_3$), 28.7 (CH$_2$*C*H$_2$CH$_2$), 37.6 (O=C*C*H$_2$), 43.1 (CH$_2$*C*HPh), 44.0 (N*C*H$_2$), 64.3 (N*C*HPh), 94.7 (*C*HNO$_2$), 126.9 (*C*H Arom.), 126.9 (*C*H Arom.), 128.5 (*C*H Arom.), 129.2 (*C*H Arom.), 129.4 (*C*H Arom.), 129.5 (*C*H Arom.), 136.6 (*C*q Arom.), 136.7 (*C*q Arom.), 168.2 (*C*=O); *m/z* (CI$^+$) 353 (M+H$^+$, 100%), 306 (M$^+$-NO$_2$, 50%), 216 (37%); HRMS: found 353.1863, $C_{21}H_{25}N_2O_3$ requires 353.1865; Anal. Cald. For $C_{21}H_{24}N_2O_3$: C, 71.57, H, 6.86, N, 7.95. Found C, 71.27, H, 6.84, N, 7.79%.

_N_-(2-Hydroxy-2-phenylethyl)benzamide 465



Prepared by general procedure F. Nitroalcohol **435** (115 mg, 0.690 mmol), ^{n}BuLi (552 µL, 2.5 M, 1.38 mmol), imine **281** (291 mg, 1.38 mmol) and TFA (184 µL, 2.41 mmol) afforded after TFA-protection crude amide **465**. Purification by flash column chromatography (Petrol:DCM 2:8) gave amide **465** (20 mg, 12%) as a white solid; mp. 145-146 ^{o}C (lit. 143-145 ^{o}C); R_f 0.45 (Petrol:DCM 2:8); IR υ_{max} (thin film) 3410 br (N-H or O-H), 3305 (N-H or O-H), 3061 w (C-H), 2933 w (C-H), 1635 s (C=O), 1618 s, 1545 s, 1061 s, 693 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.40 (1H, br, O*H*), 3.53 (1H, ddd, *J* = 5.0, 7.9, 14.1, CH_2), 3.94 (1H, ddd, *J* = 3.4, 7.1, 14.1, CH_2), 4.98 (1H, dd, *J* = 3.3, 7.8, OC*H*OH), 6.64 (1H, br, N*H*), 7.27-7.60 (8H, m, C*H* Arom.), 7.77 (2H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 47.8 (*C*H_2), 73.8 (O*C*HCH$_2$), 125.8 (*C*H Arom.), 127.0 (*C*H Arom.), 128.0 (*C*H Arom.), 128.6 (*C*H Arom.), 128.6 (*C*H Arom.), 131.7 (*C*H Arom.), 134.0 (*C*q Arom.), 141.7 (*C*q Arom.), 168.7 (*C*=O); *m/z* (CI^{+}) 242 (M+H^{+}, 10%), 224 (M-OH^{-}, 100%), 105 (31%); HRMS: found 242.11844, $C_{15}H_{15}NO_2$ requires 242.11810. Data in agreement to the one reported.[202]

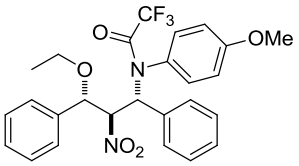
2,2,2-Trifluoro-_N_-((1_R_*,2_R_*,3_S_*)-3-methoxy-2-nitro-1,3-diphenylpropyl)-_N_-(4-methoxyphenyl)acetamide 472



Prepared by general procedure F. Nitroalkane **436** (44 mg, 0.24 mmol), ^{n}BuLi (96 µL, 2.5 M, 0.24 mmol), imine **281** (101 mg, 0.480 mmol) and TFA (64 µL, 0.840 mmol) afforded after TFA-protection crude trifluoroacetamide **472**. Purification by flash column chromatography (Petrol:Et_2O 4:1) gave trifluoroacetamide **472** (83 mg, 71%) as a white solid; mp. 69-70 ^{o}C; R_f 0.32 (Petrol:Et_2O 4:1); IR υ_{max} (thin film) 2937 w (C-H), 2837 w (C-H), 1692 s (C=O), 1557 s (N=O), 1509 s, 1457 w, 1254 m, 1203 s, 1182 s, 1151 s, 1096 m, 1026 m, 842 m, 754 m, 733 m, 699 s, 659 m cm^{-1}; ^{1}H NMR

(600 MHz) δ 3.24 (3H, s, CHOCH_3), 3.82 (3H, s, OCH_3), 5.06 (1H, d, J = 8.4, CHOCH$_3$), 5.38 (1H, dd, J = 10.9, 8.5, CHNO$_2$), 6.01 (1H, dd, J = 8.8, 2.6, CH Arom.), 6.54 (1H, dd, J = 8.8, 3.0, CH Arom.), 6.89 (1H, d, J = 11.0, CHN), 6.92 (2H, m, CH Arom.), 7.00 (1H, dd, J = 8.7, 3.0, CH Arom.), 7.16 (2H, app t, J = 7.7, CH Arom.), 7.25 (1H, m, CH Arom.), 7.36-7.44 (5H, m, CH Arom.), 7.73 (1H, dd, J = 8.8, 2.6, CH Arom.); ^{13}C NMR (150 MHz) δ 55.4 (OCH$_3$), 57.0 (CHOCH$_3$), 61.7 (CHN), 84.7 (CHOCH$_3$), 89.5 (CHNO$_2$), 113.5 (CH Arom.), 113.6 (CH Arom.), 116.6 (q, J = 290.1, CF$_3$), 126.8 (Cq Arom.), 127.7 (CH Arom.), 128.4 (CH Arom.), 128.7 (CH Arom.), 129.3 (CH Arom.), 129.3 (CH Arom.), 129.5 (CH Arom.), 131.4 (CH Arom.), 132.9 (Cq Arom.), 133.5 (CH Arom.), 135.6 (CH Arom.), 157.9 (q, J = 35.7, C=OCF$_3$), 160.1 (Cq Arom.); ^{19}F NMR (282 MHz) δ -67.82 (3F, s, CF_3); *m/z* (EI$^+$) 488 (M$^+$, 5%), 219 (PMPNHTFA$^+$, 8%), 149 (14%), 121 (PhCH-OMe$^+$, 100%); HRMS: found 488.15642, $C_{22}H_{26}N_2O_5$ requires 488.15535; Anal. Cald. For $C_{22}H_{26}N_2O_5$: C, 61.47, H, 4.75, N, 5.74. Found C, 61.60, H, 5.05, N, 5.63%.

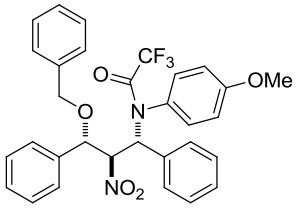
_N_-((1_R_*,2_R_*,3_S_*)-3-ethoxy-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide 473



Prepared by general procedure F. Nitroalkane **438** (110 mg, 0.560 mmol), ^{n}BuLi (224 µL, 2.5 M, 0.560 mmol), imine **281** (236 mg, 1.12 mmol) and TFA (150 µL, 1.96 mmol) afforded after TFA-protection crude trifluoroacetamide **473**. Purification by flash column chromatography (Petrol:Et$_2$O 4:1) gave trifluoroacetamide **473** (219 mg, 78%) as a yellow oil; R$_f$ 0.36 (Petrol:Et$_2$O 4:1); IR υ_{max} (thin film) 2977 w (C-H), 1694 s (C=O), 1608 w, 1556 s (N=O), 1510 s, 1457 m, 1370 w (N-O), 1300 m, 1254 m, 1203 s, 1182 s, 1152 s, 1092 m, 1075 m, 1032 m, 912 w, 876 w, 843 m, 783 m, 755 m, 733 s, 699 s cm^{-1}; ^{1}H NMR (600 MHz) δ 1.17 (3H, t, J = 7.1, CH_3), 3.40 (2H, m, OCH_2CH$_3$), 3.82 (3H, s, OCH_3), 5.13 (1H, d, J = 8.4, CHO), 5.38 (1H, dd, J = 10.9, 8.5, CHNO$_2$), 6.01 (1H, dd, J = 9.1, 2.4, CH Arom.), 6.55 (1H, dd, J = 8.9, 3.1, CH Arom.), 6.83 (1H, d, J = 10.9, CHN), 6.92 (2H, m, CH Arom.), 7.00 (1H, dd, J = 8.8, 3.0, CH Arom.), 7.16 (2H, m, CH Arom.), 7.25 (2H, m, CH Arom.), 7.38 (5H, m,

C*H* Arom.), 7.74 (1H, dd, *J* = 8.7, 2.5, C*H* Arom.); ^{13}C NMR (150 MHz) δ 14.6 (*C*H$_3$), 55.4 (O*C*H$_3$), 61.7 (*C*HN), 65.2 (O*C*H$_2$CH$_3$), 83.2 (*C*HO), 89.9 (*C*HNO$_2$), 113.5 (*C*H Arom.), 113.6 (*C*H Arom.), 116.4 (q, *J* = 288.5, *C*F$_3$), 126.8 (*C*q Arom.), 127.6 (*C*H Arom.), 128.4 (*C*H Arom.), 128.7 (*C*H Arom.), 129.2 (*C*H Arom.), 129.3 (*C*H Arom.), 131.7 (*C*H Arom.), 133.4 (*C*q Arom.), 133.5 (*C*H Arom.), 136.4 (*C*q Arom.), 157.7 (q, *J* = 35.0, *C*=O), 160.2 (*C*q Arom.); ^{19}F NMR (282 MHz) δ -67.31 (3F, s, C*F*$_3$); *m/z* (CI$^+$) 502 (M$^+$, 27%), 410 (M$^+$-EtOH-NO$_2$, 24%), 135 (100%); HRMS: found 502.17064, $C_{26}H_{25}F_3N_2O_5$ requires 502.17101.

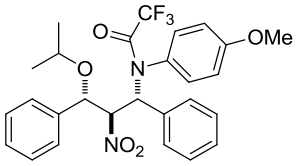
_N_-((1_R_*,2_R_*,3_S_*)-3-(benzyloxy)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide 474



Prepared by general procedure F. Nitroalkane **439** (160 mg, 0.620 mmol), ^{n}BuLi (248 μL, 2.5 M, 0.620 mmol), imine **281** (262 mg, 1.24 mmol) and TFA (166 μL, 2.17 mmol) afforded after TFA-protection crude trifluoroacetamide **474**. Purification by flash column chromatography (Petrol:Et$_2$O 9:1) gave trifluoroacetamide **474** (224 mg, 64%) as a yellow oil; R$_f$ 0.26 (Petrol:Et$_2$O 9:1); IR υ$_{max}$ (thin film) 3035 w (C-H), 1696 s (C=O), 1557 s (N=O), 1510 s, 1456 w, 1348 w (N-O), 1300 w, 1254 m, 1206 s, 1183 s, 1169 s, 1156 s, 1069 w, 1029 w, 912 w, 842 w, 756 w, 734 m, 700 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.78 (3H, s, OC*H*$_3$), 4.33 (1H, d, *J* = 10.9, C*H*$_2$), 4.53 (1H, d, *J* = 10.9, C*H*$_2$), 5.22 (1H, d, *J* = 6.7, C*H*O), 5.50 (1H, dd, *J* = 11.0, 6.8, C*H*NO$_2$), 5.96 (1H, dd, *J* = 8.8, 2.5, Arom. C*H*), 6.50 (1H, dd, *J* = 8.8, 3.0, C*H* Arom.), 6.70 (1H, d, *J* = 11.0, C*H*N), 6.82 (1H, dd, *J* = 8.8, 3.0, C*H* Arom.), 6.94 (2H, d, *J* = 7.4, C*H* Arom.), 7.17 (2H, m, C*H* Arom.), 7.25 (2H, m, C*H* Arom.), 7.30 (5H, m, C*H* Arom.), 7.47 (3H, m, C*H* Arom.), 7.52 (2H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 55.3 (O*C*H$_3$), 61.0 (*C*HN), 71.5 (*C*H$_2$), 81.7 (*C*HO), 90.0 (*C*HNO$_2$), 113.3 and 113.6 (*C*H Arom.), 116.1 (q, *J* = 288.7, *C*F$_3$), 126.4 (*C*q Arom.), 127.9, 128.2, 128.4, 128.4, 128.7, 128.9, 129.0, 129.3, 129.6, 131.4 and 133.2 (*C*H Arom.), 133.4, 135.4 and 136.3 (*C*q Arom.), 157.8 (q, *J* = 35.2, *C*=O), 160.1 (*C*q Arom.); ^{19}F NMR (282 MHz)

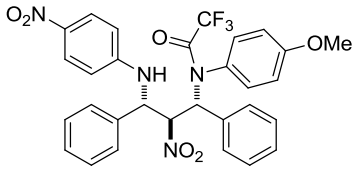
δ -67.47 (3F, s, CF_3); *m/z* (CI$^+$) 564 (M$^+$, 100%), 410 (M$^+$-BnOH-NO_2, 57%), 197 (28%); HRMS: found 564.18742, $C_{31}H_{27}F_3N_2O_5$ requires 564.18666.

2,2,2-Trifluoro-*N*-((1*R,2*R**,3*S**)-3-isopropoxy-2-nitro-1,3-diphenylpropyl)-*N*-(4-methoxyphenyl)acetamide 475**



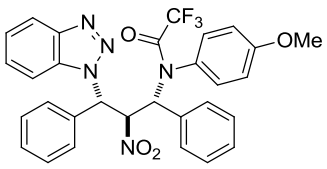
Prepared by general procedure F. Nitroalkane **440** (95 mg, 0.45 mmol), ^{n}BuLi (180 µL, 2.5 M, 0.450 mmol), imine **281** (190 mg, 0.900 mmol) and TFA (121 µL, 1.58 mmol) afforded after TFA-protection crude trifluoroacetamide **475**. Purification by flash column chromatography (Petrol:Et_2O 4:1) gave trifluoroacetamide **475** (186 mg, 80%) as a yellow oil; R_f 0.36 (Petrol:Et_2O 4:1); IR υ_{max} (thin film) 2976 w (C-H), 1695 s (C=O), 1556 s (N=O), 1510 s, 1457 w, 1373 w (N-O), 1300 w, 1254 m, 1203 s, 1168 s, 1153 s, 1120 m, 1090 m, 1067 m, 1034 m, 911 w, 843 m, 757 m, 733 m, 700 s cm^{-1}; ^{1}H NMR (600 MHz) δ 1.16 (6H, d, *J* = 6.2, C*H*$_3$), 3.53 (2H, m, OC*H*(CH_3)$_2$), 3.83 (3H, s, OC*H*$_3$), 5.24 (1H, d, *J* = 7.7, C*H*O), 5.43 (1H, dd, *J* = 10.7, 7.7, C*H*NO_2), 6.07 (1H, d, *J* = 8.7, C*H* Arom.), 6.58 (1H, dd, *J* = 8.9, 3.0, C*H* Arom.), 6.75 (1H, d, *J* = 10.8, C*H*N), 6.95 (2H, m, C*H* Arom.), 6.99 (1H, dd, *J* = 8.8, 3.0, C*H* Arom.), 7.17 (2H, m, C*H* Arom.), 7.26 (2H, m, C*H* Arom.), 7.38 (5H, m, C*H* Arom.), 7.70 (1H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 19.6 (CH*C*H_3), 23.0 (CH*C*H_3), 55.4 (O*C*H_3), 61.1 (Ph*C*HO), 69.3 (O*C*H(CH_3)$_2$), 80.2 (*C*HN), 90.4 (*C*HNO_2), 113.5 (*C*H Arom.), 113.6 (*C*H Arom.), 116.3 (q, *J* = 288.7, *C*F_3), 126.8 (*C*q Arom.), 127.6 (*C*H Arom.), 128.4 (*C*H Arom.), 128.8 (*C*H Arom.), 129.1 (*C*H Arom.), 129.3 (*C*H Arom.), 129.3 (*C*H Arom.), 131.7 (*C*H Arom.), 133.5 (*C*H Arom.), 133.7 (*C*q Arom.), 136.5 (*C*q Arom.), 157.5 (q, *J* = 35.4, *C*=O), 160.2 (*C*q Arom.); ^{19}F NMR (282 MHz) δ -67.24 (3F, s, C*F*$_3$); *m/z* (CI$^+$) 516 (M$^+$, 32%), 410 (M$^+$-IPA-NO_2, 100%), 308 (24%); HRMS: found 516.18577, $C_{27}H_{27}F_3N_2O_5$ requires 516.18666.

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R,2*S**,3*S**)-2-nitro-3-((4-nitrophenyl)amino)-1,3-diphenylpropyl)acetamide 478**



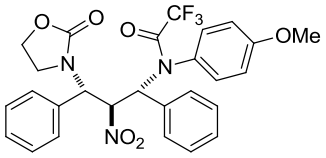
Prepared by general procedure F. Nitroalkane **444** (114 mg, 0.400 mmol), ^{n}BuLi (160 μL, 2.5 M, 0.400 mmol), imine **281** (169 mg, 0.800 mmol) and TFA (31 μL, 0.400 mmol) afforded after TFA-protection crude trifluoroacetamide **478**. Purification by flash column chromatography (Petrol:Me_2CO 4:1) gave trifluoroacetamide **478** (40 mg, 17%) as a yellow solid; mp. 141-142 ^{o}C, R_f 0.30 (Petrol:Me_2CO 4:1); IR υ_{max} (thin film) 3332 w (N-H), 1693 m (C=O), 1595 m, 1558 m (N=O), 1510 m, 1287 s, 1258 m, 1209 s, 1180 s, 1160 s, 1109 s, 1038 m, 838 s, 754 m, 733 m, 698 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.77 (3H, s, OC*H*$_3$), 5.33 (1H, dd, *J* = 9.4, 3.1, C*H*NH), 5.75 (1H, dd, *J* = 10.8, 3.1, C*H*NO_2), 5.97 (1H, app d, *J* = 8.8, C*H* Arom.), 6.18 (1H, d, *J* = 9.4, N*H*), 6.34 (1H, app d, *J* = 8.8, C*H* Arom.), 6.37 (1H, d, *J* = 10.8, C*H*NC=O), 6.54 (1H, dd, *J* = 8.8, 3.0, C*H* Arom.), 6.67 (1H, app d, *J* = 9.1, C*H* Arom.), 6.72 (1H, dd, *J* = 8.8, 3.1, C*H* Arom.), 7.00 (2H, m, C*H* Arom.), 7.24 (2H, app t, *J* = 7.3, C*H* Arom.), 7.33 (1H, app t, *J* = 7.5, C*H* Arom.), 7.40-7.48 (5H, m, C*H* Arom.), 8.09 (2H, app d, *J* = 9.1, C*H* Arom.); ^{13}C NMR (150 MHz) δ 55.5 (O*C*H$_3$), 58.0 (*C*HNH), 60.4 (*C*HNC=O), 90.0 (*C*HNO_2), 112.5 (*C*H Arom.), 113.4 (*C*H Arom.), 113.7 (*C*H Arom.), 116.0 (q, *J* = 288.3, *C*F_3), 126.3, 127.0, 128.7, 128.9, 129.6, 129.6, 129.8, 130.1 and 132.5 (*C*H Arom.), 133.2 (*C*q Arom.), 135.0 (*C*q Arom.),139.6 (*C*q Arom.), 150.8 (*C*q Arom.), 158.8 (q, *J* = 35.8, *C*=OCF_3), 160.4 (*C*q Arom.); ^{19}F NMR (282 MHz) δ -67.41 (3F, s, C*F*$_3$); *m/z* (EI$^-$) 593 (M-H$^+$, 75%), 547 (M-HNO_2^+, 100%); HRMS: found 593.1653, $C_{30}H_{24}F_3N_4O_6$ requires 593.1648; Anal. Cald. For $C_{30}H_{25}F_3N_4O_6$: C, 60.61, H, 4.24, N, 9.42. Found C, 60.33, H, 4.21, N, 9.39%.

_N_-((1_R_*,2_R_*,3_S_*)-3-(1_H_-benzo[_d_][1,2,3]triazol-1-yl)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide 482



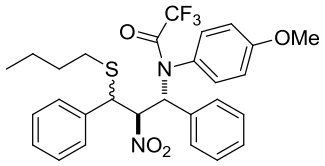
Prepared by general procedure F. Nitroalkane **446** (111 mg, 0.410 mmol), ^{n}BuLi (164 µL, 2.5 M, 0.410 mmol), imine **281** (173 mg, 0.820 mmol) and TFA (110 µL, 1.44 mmol) afforded after TFA-protection crude trifluoroacetamide **482**. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave trifluoroacetamide **482** (23 mg, 10%, 47% based on recovered starting material) as a colourless oil; R_f 0.13 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2958 w (C-H), 2926, 2856, 1694 s (C=O), 1557 s (N=O), 1510 s, 1455 m, 1409 w, 1366 w (N-O), 1300 m, 1254 m, 1207 s, 1180 s, 1163 s, 1036 m, 841 m, 775 m, 744 s, 734 s, 701 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.74 (3H, s, OC*H*$_3$), 5.87 (1H, d, J = 6.3, C*H*NC=O), 6.02 (1H, dd, *J* = 8.8, 2.4, C*H* Arom.), 6.08 (1H, d, *J* = 10.7, NC*H*), 6.39 (1H, dd, *J* = 8.8, 2.9, C*H* Arom.), 6.75 (2H, d, *J* = 7.7, C*H* Arom.), 6.80 (1H, dd, *J* = 8.8, 2.9, C*H* Arom.), 7.16 (3H, m, C*H* Arom.), 7.32 (1H, m, C*H*NO_2), 7.39 (7H, m, C*H* Arom.), 7.52 (2H, s, C*H* Arom.), 8.01 (1H, d, *J* = 8.3, C*H* Arom.); ^{13}C NMR (150 MHz) δ 55.3 (O*C*H_3), 63.0 (O=CNC*H*), 63.9 (NC*H*), 86.0 (C*H*NO_2), 109.1 (*C*H Arom.), 113.2 (*C*H Arom.), 113.8 (*C*H Arom.), 115.9 (q, *J* = 288.6, *C*F_3), 120.2 (*C*H Arom.), 124.4 (*C*H Arom.), 126.9 (*C*H Arom.), 127.2 (*C*q Arom.), 127.9 (*C*H Arom.), 128.4 (*C*H Arom.), 129.0 (*C*H Arom.), 129.2 (*C*H Arom.), 129.6 (*C*H Arom.), 129.8 (*C*q Arom.), 129.9 (*C*H Arom.), 130.2 (*C*H Arom.), 131.4 (*C*H Arom.), 131.7 (*C*H Arom.), 132.2 (*C*q Arom.), 132.6 (*C*H Arom.), 132.5 (*C*q Arom.), 145.8 (*C*q Arom.), 158.2 (q, *J* = 35.9, O=*C*CF_3), 159.9 (*C*q Arom); ^{19}F NMR (282 MHz) δ -67.86 (3F, s, C*F*$_3$); *m/z* (EI$^+$) 575 (M$^+$, 18%), 410 (M$^+$-$C_6H_4N_3$-HNO_2, 25%), 357 (M$^+$-PMP-N-TFA, 100%), 282 (39%), 180 (65%); HRMS: found 575.17786, $C_{30}H_{24}F_3N_5O_4$ requires 575.17749.

2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R,2*R**,3*S**)-2-nitro-3-(2-oxooxazolidin-3-yl)-1,3-diphenylpropyl)acetamide 480**



Prepared by general procedure F. Nitroalkane **447** (134 mg, 0.570 mmol), ^{n}BuLi (248 µL, 2.5 M, 0.620 mmol), imine **281** (240 mg, 1.14 mmol) and TFA (153 µL, 2.00 mmol) afforded after TFA-protection crude trifluoroacetamide **480**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave trifluoroacetamide **480** (101 mg, 33%) as a white solid; mp. 202-203 ^{o}C; R_f 0.21 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2926 w (C-H), 1748 s (C=O), 1695 s (C=C), 1557 s (N=O), 1511 s, 1412 m, 1376 w (N-O), 1301 w, 1252 s, 1207 s, 1181 s, 1034 m, 911 w, 842 w, 760 w, 734 m, 703 m cm^{-1}; ^{1}H NMR (600 MHz, 60 ^{o}C) δ 3.22 (1H, dt, *J* = 8.2, 7.3, NC*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 3.82 (1H, ddd, *J* = 12.2, 8.3, 3.9, NC*H*$_2$), 4.25 (1H, ddd, *J* = 12.8, 9.1, 4.0, OC*H*$_2$), 4.32 (1H, dt, *J* = 9.5, 8.6, OC*H*$_2$), 5.56 (1H, d, *J* = 10.3, CH$_2$NC*H*), 5.77 (1H, d, *J* = 7.8, O=CNC*H*), 6.55 (1H, dd, *J* = 9.9, 7.9, C*H*NO$_2$), 6.66 (1H, dd, *J* = 8.9, 2.8, C*H* Arom.), 6.71 (1H, m, C*H* Arom.), 6.80 (1H, dd, *J* = 8.9, 2.9, C*H* Arom.), 7.04 (2H, app. d, *J* = 7.6, C*H* Arom.), 7.09 (1H, app. d, *J* = 8.1, C*H* Arom.), 7.21 (2H, app. t, *J* = 7.7, C*H* Arom.), 7.31 (1H, m, C*H* Arom.), 7.37 (5H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 42.5 (N*C*H$_2$), 55.4 (O*C*H$_3$), 59.1 (*C*HNCH$_2$), 62.4 (O*C*H$_2$), 67.2 (*C*HNCOCF$_3$), 85.8 (*C*HNO$_2$), 113.4 (*C*H Arom.), 114.4 (*C*H Arom.), 116.0 (q, *J* = 288.9, *C*F$_3$), 128.3 (*C*H Arom.), 128.5 (*C*H Arom.), 128.5 (*C*q Arom), 129.1 (*C*H Arom.), 129.5 (*C*H Arom.), 129.8 (*C*H Arom.), 130.3 (*C*H Arom.), 131.5 (*C*H Arom.), 131.7 (*C*q Arom), 131.9 (*C*H Arom.), 132.5 (Arom *C*q), 158.2 (O*C*=O), 158.6 (q, *J* = 35.9, O=*C*CF$_3$), 160.1 (*C*q Arom); ^{19}F NMR (282 MHz) δ -67.63 (3F, s, C*F*$_3$); *m/z* (ESI^{+}) 544 (M+H^{+}, 55%), 497 (M^{+}-NO$_2$, 100%), 325 (M^{+}-PMPNTFA, 40%), 308 (PhCHN(TFA)PMP, 40%); HRMS: found 544.1682, $C_{27}H_{25}F_3N_3O_6$ requires 544.1695; Anal. Cald. For $C_{27}H_{24}F_3N_3O_6$: C, 59.67, H, 4.45, N, 7.73. Found C, 59.43, H, 4.51, N, 7.44%.

_N_-((1_R_*,2_R_*)-3-(butylthio)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide 485

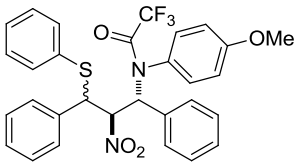


Prepared by general procedure F. Nitroalkane **448** (92 mg, 0.39 mmol), ^{n}BuLi (156 µL, 2.5 M, 0.390 mmol), imine **281** (163 mg, 0.780 mmol) and TFA (105 µL, 1.37 mmol) afforded after TFA-protection crude trifluoroacetamide **485**. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave trifluoroacetamide **485** (118 mg, 56%) as a yellow oil, R_f 0.44 (Petrol:Et_2O 9:1); diastereoisomer ratio (60:40) calculated by C*H*S signal, δ major = 4.49, δ minor = 4.44; IR υ_{max} (thin film) 2960 w (C-H), 1697 s (C=O), 1557 s (N=O), 1510 s (C=C), 1456 w, 1364 w (N-O), 1301 w, 1255 m, 1208 s, 1181 s, 1165 s, 1035 w, 840 w, 734 w, 700 m cm^{-1}; ^{1}H NMR (600 MHz) δ 0.86 (3H, t, *J* = 7.4, CH_3), 1.31-1.57 (4H, m, CH_2), 2.32 (2H, t., *J* = 7.4, SCH_2), 3.82 (3H, s, OCH_3), 4.49 (1H, d, *J* = 6.2, PhC*H*S), 5.64 (1H, dd, *J* = 10.4, 6.2, C*H*NO_2), 6.04 (1H, dd, *J* = 8.8, 2.7, C*H* Arom.), 6.40 (1H, d, *J* = 10.3, PhC*H*N), 6.56 (1H, dd, *J* = 8.8, 2.9, C*H* Arom.), 6.93-7.44 (10H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 13.5 (*C*H_3), 21.8, 30.5, 31.7 (*C*H_2), 49.5 (Ph*C*HS), 55.4 (O*C*H_3), 62.0 (Ph*C*HN), 89.8 (*C*HNO_2), 113.7, 113.8 (*C*H Arom.), 116.4 (q, *J* = 288.4, *C*F_3), 126.7 (*C*q Arom.), 128.1, 128.5, 128.7, 128.8, 128.9, 128.9, 129.3, 129.6, 131.2, 132.9 (*C*H Arom.), 133.0, 136.0, 137.4 (*C*q Arom.), 158.3 (q, *J* = 35.6, O=*C*CF_3), 160.2 (*C*q Arom.); ^{19}F NMR (282 MHz) δ -67.71 (3F, s, C*F*$_3$); *m/z* (EI$^+$) 547 (M+H$^+$, 4%), 500 (M$^+$-NO_2, 52%), 457 (M$^+$-BuS, 100%), 193 (38%); HRMS: found 547.18784, $C_{28}H_{30}F_3N_2O_4S$ requires 547.18833; Anal. Cald. For $C_{28}H_{29}F_3N_2O_4S$: C, 61.53, H, 5.35, N, 5.13. Found C, 61.14, H, 5.48, N, 5.33%.

Minor diastereomer: ^{1}H NMR (600 MHz) δ 0.84 (3H, t, *J* = 7.4, CH_3), 1.31-1.57 (4H, m, CH_2), 2.45 (2H, td., *J* = 7.1, 2.5, SCH_2), 3.82 (3H, s, OCH_3), 4.44 (1H, d, *J* = 4.6, PhC*H*S), 5.59 (1H, br. d, *J* = 9.6, PhC*H*N), 6.24 (1H, dd, *J* = 10.4, 4.6, C*H*NO_2), 6.63 (1H, d, *J* = 8.6, C*H* Arom.), 6.74 (1H, dd, *J* = 8.8, 2.9, C*H* Arom.), 6.83 (1H, dd, *J* = 8.8, 3.0, C*H* Arom.), 6.93-7.44 (9H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 13.5 (*C*H_3), 22.0, 31.0, 32.4 (*C*H_2), 49.9 (Ph*C*HS), 55.4 (O*C*H_3), 67.9 (Ph*C*HN), 92.4 (*C*HNO_2), 113.3, 114.6 (*C*H Arom.), 116.2 (q, *J* = 288.4, *C*F_3), 128.5, 128.7, 129.3,

129.6, 130.6, 130.7 (*C*H Arom.), 133.5 (*C*q Arom.), 158.3 (q, *J* = 35.6, O=*C*CF_3), 160.1 (*C*q Arom.), 6 *C*H and 3 *C*q peaks missing; ^{19}F NMR (282 MHz) δ -67.73 (3F, s, CF_3).

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R,2*R**)-2-nitro-1,3-diphenyl-3-(phenylthio)propyl)acetamide 486**



Prepared by general procedure F. Nitroalkane **449** (125 mg, 0.480 mmol), ^{n}BuLi (192 µL, 2.5 M, 0.480 mmol), imine **281** (203 mg, 0.920 mmol) and TFA (129 µL, 1.68 mmol) afforded after TFA-protection crude trifluoroacetamide **486**. Purification by flash column chromatography (Petrol:Et_2O 4:1) gave trifluoroacetamide **486** (129 mg, 47%) as an orange solid, mp. 51-52 ^{o}C; R_f 0.25 (Petrol:Et_2O 9:1); diastereoisomer ratio (65:35) calculated by C*H*S signal, δ major = 4.76, δ minor = 4.70; IR υ_{max} (thin film) 3063 w (C-H), 3032 w, 2964 w, 2935 w, 2840 w, 1695 s (C=O), 1557 s (N=O), 1509 s (C=C), 1301 w, 1254 m, 1208 s, 1180 s, 1166 s, 1033 m, 840 m, 733 m, 699 s cm^{-1}; ^{1}H NMR (600 MHz) δ 3.79 (3H, s, OCH_3), 4.76 (1H, d, *J* = 5.1, PhC*H*S), 5.69 (1H, d, *J* = 9.8, PhC*H*N), 6.35 (1H, dd, *J* = 9.8, 5.1, C*H*NO_2), 6.65-7.40 (19H, m, Arom. C*H*); ^{13}C NMR (150 MHz) δ 54.0 (Ph*C*HS), 55.4 (O*C*H_3), 67.9 (Ph*C*HN), 92.2 (*C*HNO_2), 113.4 and 114.5 (*C*H Arom.), 116.1 (q, *J* = 288.6 and 288.3, *C*F_3), 126.7 (*C*q Arom.), 127.7, 128.0, 128.5, 128.7, 128.8, 128.8, 128.9, 129.2, 129.4, 129.5, 129.7, 129.8, 130.5, 130.8, 130.9, 131.2, 132.9 and 134.2 (*C*H Arom.), 132.0, 133.1, 133.8, 135.5, 135.6 and 137.0 (*C*q Arom.), 158.4 (q, *J* = 35.6 and 35.8, O=*C*CF_3), 160.1 (*C*q Arom.); ^{19}F NMR (282 MHz) δ -67.84 (3F, s, CF_3); *m/z* (EI^{+}) 566 (M^{+}, 10%), 457 (M^{+}-PhS, 38%), 308 (64%), 301 (M^{+}-NO_2-PMP-NH-TFA, 100%), 199 (44%); HRMS: found 566.14870, $C_{30}H_{25}F_3N_2O_4S$ requires 566.14816.

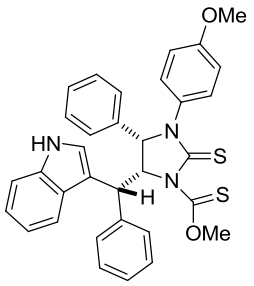
Minor diastereomer: ^{1}H NMR (600 MHz) δ 3.80 (3H, s, OCH_3), 4.70 (1H, d, *J* = 6.1, PhC*H*S), 5.79 (1H, dd, *J* = 10.0, 6.0, C*H*NO_2), 6.01 (1H, dd, *J* = 8.8, 2.0, C*H* Arom.), 6.43 (1H, d, *J* = 10.0, PhC*H*N), 6.53 (1H, dd, *J* = 8.8, 2.9, C*H* Arom.), 6.65-7.40 (17H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 52.9 (Ph*C*HS), 55.4 (O*C*H_3), 62.0

(Ph*C*HN), 88.8 (*C*HNO$_2$), 113.7 and 113.8 (*C*H Arom.), 116.3 (q, *J* = 288.6 and 288.3, *C*F$_3$), 158.4 (q, *J* = 35.6 and 35.8, O=*C*CF$_3$), 160.2 (*C*q Arom.), the rest of the ^{13}C peaks could not be distinguished between the two diastereomers; ^{19}F NMR (282 MHz) δ -67.58 (3F, s, C*F*$_3$).

General procedure G for the synthesis of 2-thioxoimidazolidines

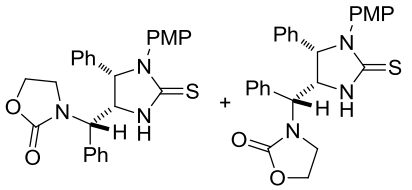
A solution of nitroalkane (1.00 mmol) in THF (10 mL), was cooled to -78 °C and ^{n}BuLi (1.10 mmol, of a 2.5 M solution in hexanes) was added dropwise. The orange mixture was stirred at this temperature for 10 min before the corresponding imine (2.00 mmol) in THF (4 mL) was added *via* cannula. The mixture was stirred for 10 min before a 1:1 mixture of TFA:THF (3.50 mmol TFA) was added dropwise. The mixture was stirred at this temperature for a further 1 h, then warmed to rt over 5 min and quenched with saturated aqueous NaHCO$_3$ (10 mL) extracted with Et$_2$O (3x10 mL), dried over MgSO$_4$ and concentrated *in vacuo* to leave crude *β*-nitroamine. A sample was taken for ^{1}H NMR analysis and the rest of the crude product was dissolved in EtOH (30 mL) and EtOAc (30 mL) and then an aqueous solution of 6 M HCl (10 mL, 60 mmol) was added followed by Zn dust (1.96 g, 30 mmol) in 3 portions over 1 h. The mixture was stirred vigorously for 1 h and then the solvents were removed *in vacuo*. The residue was neutralised with saturated aqueous Na$_2$CO$_3$ and extracted with EtOAc (3x20 mL), washed with brine (10 mL), dried over MgSO$_4$ and concentrated *in vacuo* to leave crude diamine. The diamine was purified further with column chromatography to remove by-product *para*-anisidine and was then reacted with thiophosgene without further purification. The diamine (0.25 mmol) was dissolved in DCM (7 mL) and MeOH (3 mL) and saturated aqueous NaHCO$_3$ (1 mL) and H$_2$O (1 mL) were added. The mixture was stirred for 5 min at rt and then CSCl$_2$ (29 μL, 0.37 mmol) was added and the mixture stirred for 24 h. Water (10 mL) was then added and the mixture extracted with DCM (3x10 mL), dried over MgSO$_4$ and evaporated *in vacuo* to give crude 2-thioxoimidazolidine that was purified by flash column chromatography.

(4*S,5*R**)-O-methyl 5-((*R**)-(1*H*-indol-3-yl)(phenyl)methyl)-3-(4-methoxyphenyl)-4-phenyl-2-thioxoimidazolidine-1-carbothioate 488**



Prepared by general procedure G. Nitroalkane **429** (222 mg, 0.830 mmol), ^{n}BuLi (0.913 mmol), imine **281** (350 mg, 1.66 mmol) and TFA (220 μL, 2.91 mmol) afforded after reduction and column chromatography (Petrol:EtOAc 1:1, R_f 0.29) the crude diamine (296 mg, 80%). Subsequent reaction of the diamine (0.66 mmol) with $CSCl_2$ (90 μL, 0.99 mmol) gave crude 2-thioxoimidazolidine **488**. Purification by flash column chromatography (Petrol:EtOAc 7:3) gave 2-thioxoimidazolidine **488** (31 mg, 7%) as a brown oil, Rf 0.77 (Petrol:EtOAc 1:1); IR υ_{max} (thin film) 3338 br (N-H), 3058 w (C-H), 1512 s (C=O), 1556 s (C=C), 1450 m, 1338 m, 1322 m, 1289 m, 1245 s, 1030 m, 831 m, 742 m, 700 m cm^{-1}; ^{1}H NMR (600 MHz) δ 3.69 (3H, s, OC*H*$_3$), 3.70 (3H, s, OC*H*$_3$), 4.34 (1H, d, *J* = 10.4, PhC*H*Ar), 5.45 (1H, d, *J* = 8.7, NC*H*Ph), 6.16 (1H, dd, *J* = 8.7, 10.3, NC*H*), 6.74 (2H, m, C*H* Arom.), 6.88 (8H, m, C*H* Arom.), 7.05 (6H, m, C*H* Arom.), 2.24 (3H, m, C*H* Arom.), 8.02 (1H, s, N*H*); ^{13}C NMR (150 MHz) δ 44.2 (PhCHAr), 55.2 (ArOCH$_3$), 58.9 (OCH$_3$), 67.1 (NCH), 69.6 (NCHPh), 110.8 and 114.0 (*C*H Arom.), 115.8 (*C*q Arom.), 119.0, 119.3, 121.8, 122.1 (*C*H Arom.), 126.4 (*C*q Arom.), 126.8, 127.7, 127.7, 128.0, 128.4, 128.7 and 130.5 (*C*H Arom.), 131.5, 133.7, 135.8 and 139.7 (*C*q Arom.), 158.4 (*C*q$_{PMPC1}$), 182.2 (N*C*=S), 194.4 (O*C*=S); *m/z* (CI$^+$) 563 (M$^+$, 22%), 504 (16%), 297 (100%); HRMS: found 563.16883, $C_{33}H_{29}N_3O_2S_2$ requires 563.17012.

3-((S*)-((4R*,5S*)-1-(4-methoxyphenyl)-5-phenyl-2-thioxoimidazolidin-4-yl)(phenyl)methyl)oxazolidin-2-one 491a and **3-((R*)-((4R*,5S*)-1-(4-methoxyphenyl)-5-phenyl-2-thioxoimidazolidin-4-yl)(phenyl)methyl)oxazolidin-2-one 491b**



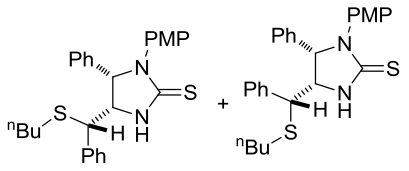
491a, major **491b**, minor

Prepared by general procedure G. Nitroalkane **447** (213 mg, 0.900 mmol), ^{n}BuLi (0.990 mmol), imine **281** (380 mg, 1.80 mmol) and TFA (241 μL, 3.15 mmol) afforded after reduction and column chromatography (Et_2O, Rf 0.27) crude diamine (106 mg, 28%). Subsequent reaction of the diamine (0.25 mmol) with $CSCl_2$ (29 μL, 0.37 mmol) gave crude 2-thioxoimidazolidines **491a** and **491b**. Purification by flash column chromatography (Petrol:Et_2O 1:1) gave 2-thioxoimidazolidines **491a** and **491b** (87 mg, 21%) as a white solid, isolated as a mixture of diastereomers, mp. 141-142 ^{o}C; R_f 0.51 (Et_2O); diastereoisomer ratio (85:15) calculated by the NCH_2 signal, δ major = 3.02, δ minor = 3.25; IR υ_{max} (thin film) 3277 br. (N-H), 2923 w (C-H), 1739 s (C=S), 1513 s (C=C), 1446 m, 1246 s, 1034 w, 705 m cm^{-1}; ^{1}H NMR (600 MHz) δ 2.05 (1H, ddd, *J* = 9.5, 8.3, 5.9, NCH_2), 3.02 (1H, dt, *J* = 9.5, 8.0, NCH_2), 3.67 (1H, d, *J* = 10.7, O=CNC*H*), 3.72 (3H, s, OCH_3), 3.92 (1H, dt, *J* = 9.4, 8.0, OCH_2), 4.02 (1H, ddd, *J* = 9.5, 8.6, 5.8, OCH_2), 5.40 (1H, br. s, N*H*), 5.46 (1H, d, *J* = 9.4, NC*H*Ph), 5.78 (1H, dd, *J* = 10.0, 9.5, C*H*NH), 6.77 (2H, app. d, *J* = 8.9, C$H_{PMPC3-H}$), 7.21 (2H, app. d, *J* = 8.9, C$H_{PMPC2-H}$), 7.25-7.40 (10H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 45.2 (NCH_2), 55.3 (OCH_3), 58.9 (NH*C*H), 61.1 (O=CN*C*H), 62.0 (OCH_2), 70.4 (N*C*HPh), 114.0 (*C*H$_{PMPC3}$), 128.0, 128.2, 128.4, 128.6, 129.1, 129.5 and 129.5 (*C*H Arom.), 131.2, 135.5, 136.5, 157.2 and 158.4 (*C*q Arom.), 183.4 (*C*=S); *m/z* (EI$^+$) 459 (M$^+$, 49%), 386 (M$^+$-IPA-NO_2, 30%), 372 (M$^+$-oxazolidonone, 50%), 297 (38%), 283 (M$^+$-PhCH($C_3H_4NO_2$), 100%); HRMS: found 459.16088, $C_{26}H_{25}N_3O_3S$ requires 459.16111.

Minor diastereomer: ^{1}H NMR (600 MHz) δ 2.42 (1H, m, NCH_2), 3.25 (1H, m, NCH_2), 3.71 (3H, s, OCH_3), 3.75 (1H, m, OCH_2), 3.85 (1H, m, OCH_2), 4.13 (1H, d, *J* = 10.0, O=CNC*H*), 5.40 (1H, d, *J* = 9.8, NC*H*Ph), 5.56 (1H, m, C*H*NH), 6.73 (2H, app. d, *J* = 8.9, C$H_{PMPC3-H}$), 7.02 (2H, app. d, *J* = 8.9, C$H_{PMPC2-H}$), 7.25-7.40 (10H, m,

C*H* Arom.), N*H* peak missing; ^{13}C NMR (150 MHz) δ 44.1 (N*C*H$_2$), 55.3 (O*C*H$_3$), 60.3 (NH*C*H), 61.1 (N*C*HPh), 61.7 (O*C*H$_2$), 114.1 (*C*H$_{PMPC3}$), 127.3 and 128.1 (*C*H Arom.), the rest of the aromatic region could not be distinguished.

(4*S,5*S**)-4-((*S**)-(butylthio)(phenyl)methyl)-1-(4-methoxyphenyl)-5-phenylimidazolidine-2-thione 492a** and **(4*S**,5*S**)-4-((*R**)-(butylthio)(phenyl)methyl)-1-(4-methoxyphenyl)-5-phenylimidazolidine-2-thione 492b**



492a **492b**

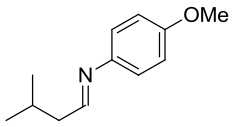
Prepared by general procedure G. Nitroalkane **448** (235 mg, 0.980 mmol), ^{n}BuLi (1.08 mmol), imine **281** (414 mg, 1.96 mmol) and TFA (262 µL, 3.43 mmol) afforded after reduction and column chromatography (Petrol:Et$_2$O 1:1, Rf 0.31) crude diamine (182 mg, 44%). Subsequent reaction of the diamine (0.43 mmol) with CSCl$_2$ (49 µL, 0.65 mmol) gave crude 2-thioxoimidazolidine **492**. Purification by flash column chromatography (Petrol:Et$_2$O 1:1) gave 2-thioxoimidazolidine **492** (89 mg, 20%) as a white solid, isolated as a mixture of diastereomers, mp. 183-184 ^{o}C; R$_f$ 0.54 (Petrol:Et$_2$O 1:1); diastereoisomer ratio (80:20) calculated by the NC*H*Ph signal, δ major = 3.14, δ minor = 3.44; IR υ$_{max}$ (thin film) 3386 br. (N-H), 2955 w (C-H), 1609 w, 1511 s, 1445 s, 1241 s, 1174 m, 1027 m, 830 m, 735 m, 697 s cm^{-1}; ^{1}H NMR (600 MHz) δ 0.68 (3H, t, *J* = 7.0, C*H*$_3$), 1.04 (4H, m, C*H*$_2$), 1.83 (1H, m, SC*H*$_2$), 1.95 (1H, m, SC*H*$_2$), 3.14 (1H, d, *J* = 11.5, C*H*S), 3.72 (3H, s, OC*H*$_3$), 4.58 (1H, ddd, *J* = 11.5, 8.4, 1.1, C*H*NH), 5.31 (1H, d, *J* = 8.4, NC*H*Ph), 5.40 (1H, br. s, N*H*), 6.77 (2H, m, C*H* Arom.), 7.17 (2H, m, C*H* Arom.), 7.23-7.38 (10H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 13.4 (*C*H$_3$), 21.6 (*C*H$_2$), 30.4 (*C*H$_2$), 30.6 (*C*H$_2$), 49.1 (*C*HS), 55.2 (O*C*H$_3$), 62.8 (NH*C*H), 71.2 (N*C*HPh), 113.9 (C*H*$_{PMPC3-H}$), 127.6, 128.3, 128.3, 128.3, 128.4, 128.9 and 129.0 (*C*H Arom.), 131.6, 134.2 and 138.8 (*C*q Arom.), 158.3 (*C*q$_{PMPC4}$), 183.4 (*C*=S); *m/z* (EI$^-$) 461 (M$^-$, 5%), 451 (30%), 437 (24%); HRMS: found 461.1765, C$_{27}$H$_{29}$N$_2$OS$_2$ requires 461.1721; Anal. Cald. For C$_{27}$H$_{30}$N$_2$OS$_2$: C, 70.09, H, 6.54, N, 6.05. Found C, 69.97, H, 6.54, N, 5.97%.

Minor diastereomer: ^{1}H NMR (600 MHz) δ 0.81 (3H, t, *J* = 7.4, C*H*$_3$), 1.27 (2H, m, C*H*$_2$), 1.38 (2H, m, C*H*$_2$), 2.28 (2H, m, SC*H*$_2$), 3.44 (1H, d, *J* = 11.2, C*H*S), 3.69 (3H, s, OC*H*$_3$), 4.85 (1H, d, *J* = 8.8, NC*H*Ph), 4.91 (1H, ddd, *J* = 11.2, 8.8, 0.9, C*H*NH), 6.70 (1H, br. s, N*H*), 6.70 (2H, m, C*H* Arom.), 7.10 (2H, m, C*H* Arom.), 7.23-7.38 (10H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 13.5 (*C*H$_3$), 21.9 (*C*H$_2$), 30.1 (*C*H$_2$), 31.2 (*C*H$_2$), 49.7 (*C*HS), 55.2 (O*C*H$_3$), 61.4 (NH*C*H), 70.6 (N*C*HPh), 113.8 (C*H*$_{PMPC3-H}$), 127.6 and 128.8 (*C*H Arom.), 131.5, 134.2 and 138.3 (*C*q Arom.), 158.3 (*C*q$_{PMPC4}$), 183.1 (*C*=S), the rest of the aromatic region could not be distinguished.

3.4.4 *Piperazirum* synthesis

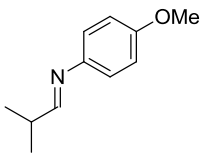
3.4.4.1 Synthesis of starting materials

(*E*)-4-Methoxy-*N*-(3-methylbutylidene)aniline 534



To a solution of *para*-anisidine (123 mg, 1.00 mmol) in DCM (5 mL), was added basic alumina (1.00 g) and the mixture cooled to -78 ^{o}C. Isovaleraldehyde (107 μL, 1.00 mmol) was then added and the mixture stirred at this temperature for 1 h, then warmed to rt, filtered and evaporated *in vacuo* to give crude imine **534** (182 mg, 95%) as a colourless oil used immediately without further purification; ^{1}H NMR (600 MHz) δ 1.02 (6H, d, *J* = 6.7, C*H*$_3$), 2.04 (1H, sept, *J* = 6.7, C*H*(CH$_3$)$_2$), 2.34 (2H, dd, *J* = 7.0, 5.4, C*H*$_2$), 3.80 (1H, s, OC*H*$_3$), 6.87 (2H, app. d, *J* = 8.9, CH$_{PMPC3-H}$), 7.02 (2H, app. d, *J* = 8.9, CH$_{PMPC2-H}$), 7.86 (1H, t, *J* = 5.4, N=C*H*); ^{13}C NMR (150 MHz) δ 22.0 (*C*H$_3$), 24.8 (*C*H$_3$), 77.7 (*C*q), 80.8 (*C*H$_2$), 170.5 (*C*=O). Data in agreement to that reported.[272]

(*E*)-4-Methoxy-*N*-(2-methylpropylidene)aniline 524



To a solution of *para*-anisidine (246 mg, 2.00 mmol) in DCM (10 mL), was added basic alumina (2.00 g) and the mixture cooled to -78 ^{o}C. Isobutyraldehyde (182 μL, 2.00 mmol) was added and the mixture stirred at this temperature for 1 h, then warmed to rt, filtered and evaporated *in vacuo* to give crude imine **524** (343 mg, 89% pure by ^{1}H NMR, 86%) as a colourless oil which was used without further purification; IR υ_{max} (thin film) 2962 w (C-H), 2869 w, 1649 m (C=C), 1503 s, 1464 m, 1441 m, 1291 m, 1239 s, 1211 m, 1179 m, 1105 m, 1034 m, 823 m, 759 m cm^{-1}; ^{1}H NMR (600 MHz) δ 1.18 (3H, d, *J* = 6.9, C*H*$_3$), 2.62 (1H, m, C*H*(CH$_3$)$_2$), 3.80 (3H, s, OC*H*$_3$), 6.87 (2H, app. d, *J* = 8.8, Arom. C*H*), 7.02 (2H, app. d, *J* = 8.8, Arom. C*H*), 7.73 (1H, d, *J* = 4.9, =C*H*); ^{13}C NMR (150 MHz) δ 19.2 (*C*H$_3$), 34.7 (*C*H), 55.4 (O*C*H$_3$), 114.1 (*C*H Arom.), 121.7 (*C*H Arom.), 145.3 (*C*q Arom.), 157.7 (*C*q Arom.), 169.4 (=*C*H); *m/z* (EI^{+}) 177 (M^{+}, 100%), 162 (M^{+}-Me, 53%); HRMS: found 177.11441 $C_{11}H_{15}NO$ requires 177.11482.

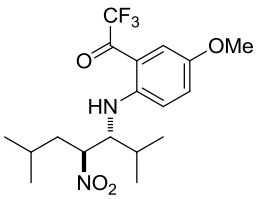
3.4.4.2 Investigation of the synthesis

General procedure H for the synthesis of trifluoroacetamides 525 and 535.

Prepared by modification of the reported method.[36] To a solution of nitroalkene (1.00 mmol) in DCM (6 mL) was added Superhydride® (1.10 mmol) and the suspension stirred at rt for 15 min. The mixture was then cooled to -78 ^{o}C and freshly prepared imine (2.00 mmol) in DCM (6 mL) was added. The reaction was stirred for 10 min before the addition of TFA (3.00 mmol) in DCM (2 mL) dropwise. The mixture was stirred at this temperature for 1 h and then quenched with brine (10 mL) at -78 ^{o}C and extracted with Et_2O (3x10 mL). The combined organics were dried over $MgSO_4$ and evaporated *in vacuo* to give crude *β*-nitroamine. A sample was taken for ^{1}H-NMR analysis and the rest of the crude product was dissolved in DCM (5 mL), cooled to 0 °C and trifluoroacetic anhydride (550 μL, 4.00 mmol) and then pyridine (320 μL, 4.00 mmol) were added dropwise. The mixture was then warmed to rt and stirred for

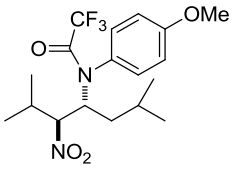
30 min. The mixture was then washed with 2 M aqueous HCl (3x10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give crude trifluoroacetamide that was further purified by flash column chromatography.

1-(2-(((3*R,4*S**)-2,6-Dimethyl-4-nitroheptan-3-yl)amino)-5-methoxyphenyl)-2,2,2-trifluoroethanone 525**



Prepared by general method H. Nitroalkene **523** (115 mg, 1.00 mmol), Superhydride® (1.10 mL, 1 M in THF, 1.10 mmol), freshly prepared imine **524** (345 mg, 2.00 mmol) and TFA (230 µL, 3.00 mmol) gave crude *β*-nitroamine **522**. Reaction with trifluoroacetic anhydride (550 µL, 4.00 mmol) and pyridine (320 µL, 4.00 mmol) for 1 h gave crude trifluoroacetamide **525**. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave trifluoroacetamide **525** (60 mg, 15%) as an orange solid; mp. 99-100 ^oC; R_f 0.61 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 3310 br (N-H), 2964 w (C-H), 1652 m (C=O), 1582 m, 1552 m (C=C), 1525 s (N-O), 1468 m, 1421 w, 1372 m (N-O), 1265 m, 1233 m, 1193 m (C-F), 1148 s (C-F), 1117 m, 1045 m cm^{-1}; ^1H NMR (600 MHz) δ 0.89 (3H, d, *J* = 6.7, C*H*$_3$), 0.90 (3H, d, *J* = 6.3, C*H*$_3$), 0.91 (3H, d, *J* = 6.6, C*H*$_3$), 1.04 (3H, d, *J* = 6.8, C*H*$_3$), 1.44 (1H, m, C*H*$_2$), 1.51 (1H, m, C*H*CH$_3$), 2.09 (1H, ddd, *J* = 14.6, 11.7, 3.5, C*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 4.10 (1H, ddd, *J* = 10.5, 7.9, 4.6, C*H*NH), 4.72 (1H, ddd, *J* = 11.7, 7.9, 2.4, C*H*NO$_2$), 6.92 (1H, app. d, *J* = 9.4, C*H* Arom.), 7.20 (2H, m, C*H* Arom.), 8.70 (1H, d, *J* = 10.4, N*H*); ^{13}C NMR (150 MHz) δ 16.3 (*C*H$_3$), 20.0 (*C*H$_3$), 20.9 (*C*H$_3$), 23.3 (*C*H$_3$), 25.1 (*C*H(CH$_3$)$_2$), 30.5 (*C*H(CH$_3$)$_2$), 38.4 (*C*H$_2$), 55.7 (O*C*H$_3$), 60.5 (*C*HNH), 88.2 (*C*HNO$_2$), 110.3 (*C*q Arom.), 112.5 (q, *J* = 4.6, *C*H Arom.), 114.0 (*C*H Arom.), 116.3 (*C*H Arom.), 117.2 (q, *J* = 291.0, *C*F$_3$), 128.4 (*C*H Arom.), 149.4 (*C*q Arom.), 150.1 (*C*q Arom.), 180.3 (q, *J* = 33.3, *C*=O); ^{19}F NMR (282 MHz) δ -69.40 (3F, s, C*F*$_3$); *m/z* (EI$^+$) 390 (M$^+$, 15%), 301 (25%), 274 (100%), 258 (36%); HRMS: found 390.175746, $C_{18}H_{25}F_3N_2O_4$ requires 390.17609; Anal. Cald. For $C_{18}H_{25}F_3N_2O_4$: C, 55.38, H, 6.45, N, 7.18. Found C, 55.43, H, 6.51, N, 6.93%.

_N_-((3_S_*,4_R_*)-2,6-dimethyl-3-nitroheptan-4-yl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide 535



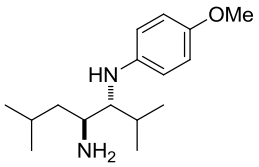
Prepared by general procedure H. Nitroalkene **530** (101 mg, 1.00 mmol), Superhydride® (1.10 mL, 1 M in THF, 1.1 mmol), freshly prepared imine **534** (282 mg, 2.0 mmol) and TFA (230 μL, 3.00 mmol) gave crude *β*-nitroamine **529**. Subsequent reaction with trifluoroacetic anhydride (550 μL, 4.00 mmol) and pyridine (320 μL, 4.00 mmol) gave crude trifluoroacetamide **535**. Purification by flash column chromatography (Toluene) gave trifluoroacetamide **535** (340 mg, 87%) as a colourless oil; R_f 0.61 (Toluene); IR υ_{max} (thin film) 2963 w (C-H), 1694 s (C=C), 1549 s (N=O), 1511 s, 1466 m, 1367 w (N-O), 1300 m, 1255 m, 1204 s, 1185 s, 1150 s, 1113 m, 1032 m, 829 m, 757 m, 735 m cm^{-1}; ^{1}H NMR (600 MHz) δ 0.89 (3H, t, *J* = 6.8, C*H*$_3$), 1.04 (3H, t, *J* = 6.4, C*H*$_3$), 1.09 (3H, t, *J* = 6.5, C*H*$_3$), 1.14 (3H, t, *J* = 6.9, C*H*$_3$), 1.47 (2H, br. s, C*H*$_2$), 1.69 (1H, m, C*H*(CH$_3$)$_2$), 2.35 (1H, m, C*H*(CH$_3$)$_2$), 3.85 (3H, s, OC*H*$_3$), 4.41 (1H, br. s, C*H*NO$_2$), 5.31 (1H,br. s, C*H*N), 6.93 (2H, app. d, *J* = 9.2, C*H* Arom.), 6.98 (2H, m, C*H* Arom.), 7.06 (2H, m, C*H* Arom.); ^{13}C NMR (150 MHz) δ 17.3 (*C*H$_3$), 19.9 (*C*H$_3$), 21.3 (*C*H$_3$), 23.3 (*C*H$_3$), 24.8 (*C*H), 29.1 (*C*H), 36.1 (*C*H$_2$), 54.3 (*C*HN), 55.5 (O*C*H$_3$), 94.1 (*C*HNO$_2$), 114.3 (*C*H Arom.), 114.4 (*C*H Arom.), 116.2 (q, *C*F$_3$, *J* = 288.5), 125.8 (*C*q Arom.), 130.4 (*C*H Arom.), 131.8 (*C*H Arom.), 158.5 (q, *C*=O, *J* = 35.6), 160.4 (*C*q Arom.); ^{19}F NMR (282 MHz) δ -67.94 (3F, s, C*F*$_3$); *m/z* (CI$^+$) 391 (M+H$^+$, 23%), 349 (15%), 288 (100%); HRMS: found 391.18488, $C_{18}H_{26}F_3N_2O_4$ requires 391.18447; Anal. Cald. For $C_{18}H_{25}F_3N_2O_4$: C, 55.38, H, 6.45, N, 7.18. Found C, 55.31, H, 6.47, N, 7.06%.

General procedure I for the synthesis of diamines 526 and 538.

Crude *β*-nitroamines **522** and **529** were prepared by general procedure H, purified quickly by flash column chromatography and reduced immediately. To a solution of *β*-nitroamine in EtOH (20 mL) and EtOAc (20 mL) was added an aqueous solution of 6 M HCl (6.60 mL, 40.0 mmol), followed by Zn dust (1.30 g, 20.0 mmol) in 3

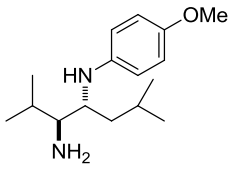
portions over 1 h. The mixture was stirred vigorously for 1 h before the solvents were removed *in vacuo*. The residue was neutralised with saturated aqueous Na_2CO_3 and extracted with EtOAc (3x20 mL), washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave the crude diamine that was further purified by flash column chromatography.

(3*R,4*S**)-*N3*-(4-Methoxyphenyl)-2,6-dimethylheptane-3,4-diamine 526**



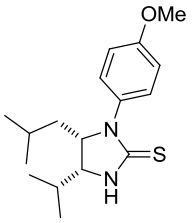
Prepared by general procedure I. Nitroalkene **523** (230 mg, 2.00 mmol), Superhydride® (2.20 mmol), imine **524** (708 mg, 4.00 mmol) and TFA (460 μL, 6.00 mmol) gave crude *β*-nitroamine **522**, that was purified quickly by column chromatography (Petrol:Et_2O 4:1). A sample was taken for ^{1}H-NMR analysis. Subsequent reaction with 6 M HCl (6.60 mL, 40.0 mmol) and Zn dust (1.30 g, 20.0 mmol) gave crude diamine **526**. Purification by flash column chromatography (DCM:MeOH 20:1) gave diamine **526** (248 mg, 50%) as a white solid; mp. 86-87 ^oC; R_f 0.29 (DCM:MeOH 20:1); IR υ_{max} (thin film) 3374 br (N-H), 2954 m (C-H), 1509 s (C=C), 1465 m, 1230 s, 1178 m, 1039 m, 815 m cm^{-1}; ^{1}H NMR (600 MHz) δ 0.91 (12H, m, C*H*$_3$), 1.21 (2H, m, C*H*$_2$), 1.81 (2H, m, C*H*(CH$_3$)$_2$), 1.81 (2H, m, N*H*$_2$), 2.93 (1H, m, C*H*NH$_2$), 3.05 (1H, m, C*H*NH), 3.15 (1H, br. S, N*H*), 3.72 (3H, s, OC*H*$_3$), 6.62 (2H, app. d, *J* = 8.7, C*H* Arom.), 6.73 (2H, app. d, *J* = 8.5, C*H* Arom.); ^{13}C NMR (150 MHz) δ 19.1 (*C*H$_3$), 20.6 (*C*H$_3$), 21.2 (*C*H$_3$), 24.3 (*C*H$_3$), 24.6 (*C*H(CH$_3$)$_2$), 31.3 (*C*H(CH$_3$)$_2$), 41.5 (*C*H$_2$), 50.9 (*C*HNH$_2$), 55.7 (O*C*H$_3$), 65.6 (*C*HNH), 113.9 (*C*H Arom.), 114.8 (*C*H Arom.), 144.2 (*C*q Arom.), 151.3 (*C*q Arom.); *m/z* (EI$^+$) 264 (M$^+$, 6%), 178 (100%); HRMS: found 264.219570, $C_{16}H_{28}N_2O$ requires 264.21962.

(3*S,4*R**)-*N*-4-(4-Methoxyphenyl)-2,6-dimethylheptane-3,4-diamine 538**



Prepared by general procedure I. Nitroalkene **530** (202 mg, 2.00 mmol), Superhydride® (2.20 mmol), imine **534** (4.00 mmol) and TFA (6.00 mmol) gave crude *β*-nitroamine **529**, that was purified quickly by column chromatography (Petrol:Et_2O 4:1). A sample was taken for ^{1}H-NMR analysis. Subsequent reaction with 6 M HCl (6.60 mL, 40.0 mmol) and Zn dust (1.30 g, 20.0 mmol) gave crude diamine **538**. Purification by flash column chromatography (DCM:MeOH 10:1) gave diamine **538** (452 mg, 85%) as a brown oil; R_f 0.50 (DCM:MeOH 10:1); IR υ_{max} (thin film) 3374 br (N-H), 2955 w (C-H), 1618 w, 1508 s (C=C), 1465 m, 1441 w, 1385 w, 1366 w, 1292 w, 1238 s, 1179 w, 1154 w, 1038 m, 816 m, 752 s cm^{-1}; ^{1}H NMR (600 MHz) δ 0.90 (3H, d, *J* = 6.5, C*H*$_3$), 0.92 (3H, d, *J* = 6.7, C*H*$_3$), 0.99 (6H, d, *J* = 6.6, C*H*$_3$), 1.21 (1H, m, C*H*$_2$), 1.35 (1H, m, C*H*$_2$), 1.59 (1H, m, C*H*(CH$_3$)$_2$), 1.80 (1H, m, C*H*(CH$_3$)$_2$), 2.53 (1H, dd, *J* = 9.1, 2.7, C*H*NH$_2$), 3.52 (1H, m, C*H*NH), 3.73 (3H, s, OC*H*$_3$), 6.57 (2H, app. d, *J* = 8.9, Arom. C*H*), 6.76 (2H, app. d, *J* = 8.9, Arom. C*H*); ^{13}C NMR (150 MHz) δ 19.6 (*C*H$_3$), 20.6 (*C*H$_3$), 21.7 (*C*H$_3$), 24.1 (*C*H$_3$), 24.7 (*C*H(CH$_3$)$_2$), 31.4 (*C*H(CH$_3$)$_2$), 37.2 (*C*H$_2$), 52.9 (*C*HNH), 55.8 (O*C*H$_3$), 59.1 (*C*HNH$_2$), 114.4 (*C*H Arom.), 115.0 (*C*H Arom.), 142.3 (*C*q Arom.), 151.6 (*C*q Arom.); *m/z* (EI$^+$) 264 (M$^+$, 5%), 192 (M$^+$-NH-CH$_2$(CH$_3$)$_2$, 100%); HRMS: found 264.22013, $C_{16}H_{28}N_2O$ requires 264.21962.

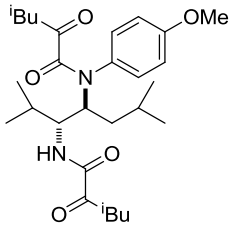
(4*R,5*S**)-4-Isobutyl-5-isopropyl-1-(4-methoxyphenyl)imidazolidine-2-thione 544**



Diamine **538** (130 mg, 0.490 mmol) was dissolved in DCM (14 mL) and MeOH (7 mL) and saturated aqueous $NaHCO_3$ (2.40 mL) and H_2O (2.40 mL) were added, stirred for 5 min at rt and then $CSCl_2$ (55 μL, 0.74 mmol) was added and the mixture stirred for 24 h. Water (20 mL) was then added and the mixture extracted with DCM

(3x20 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude 2-thioxoimidazolidine **544**. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave 2-thioxoimidazolidine **544** (130 mg, 42%) as a white solid; mp. 123-124 ^oC; R_f 0.53 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 3200 br (N-H), 2955 m (C-H), 1612 w, 1515 s (C=O), 1485 m (C=C), 1448 s, 1253 s, 1225 m, 1172 m, 1033 m, 840 m, 808 m cm^{-1}; ^1H NMR (600 MHz) δ 0.77 (3H, d, *J* = 6.6, CH_3), 0.79 (3H, d, *J* = 6.6, CH_3), 0.96 (3H, d, *J* = 6.8, CH_3), 1.05 (3H, d, *J* = 6.6, CH_3), 1.35 (1H, m, $CH_2CH(CH_3)_2$), 1.44 (1H, m, CH_2), 1.49 (1H, m, CH_2), 1.96 (1H, m, $CHCH(CH_3)_2$), 3.70 (1H, dd, *J* = 8.4, 5.4, C*H*NH), 3.82 (3H, s, OCH_3), 4.31 (1H, dt, *J* = 7.9, 5.9, NC*H*CH_2), 6.36 (1H, br. s, N*H*), 6.92 (2H, app. d, *J* = 8.9, $CH_{PMPC3\text{-}H}$), 7.22 (2H, app. d, *J* = 8.9, $CH_{PMPC2\text{-}H}$); ^{13}C NMR (150 MHz) δ 19.1 (*C*H_3), 20.6 (*C*H_3), 21.2 (*C*H_3), 24.3 (*C*H_3), 24.6 (*C*$H(CH_3)_2$), 31.3 (*C*$H(CH_3)_2$), 41.5 (*C*H_2), 50.9 (*C*HNH_2), 55.7 (O*C*H_3), 65.6 (*C*HNH), 113.9 (*C*H Arom.), 114.8 (*C*H Arom.), 144.2 (*C*q Arom.), 151.3 (*C*q Arom.); *m/z* (EI^+) 264 (M^+, 6%), 178 (100%); HRMS: found 264.219570, $C_{17}H_{26}N_2OS$ requires 264.21962; Anal. Cald. For $C_{17}H_{26}N_2OS$: C, 66.62, H, 8.55, N, 9.14. Found C, 66.30, H, 8.60, N, 9.93%.

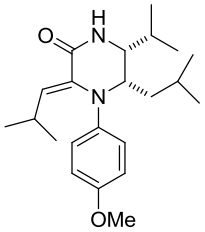
_N_-((3_R_*,4_S_*)-2,6-dimethyl-3-(4-methyl-2-oxopentanamido)heptan-4-yl)-_N_-(4-methoxyphenyl)-4-methyl-2-oxopentanamide 540[227]



To a solution of ketoacid **519** (130 mg, 1.00 mmol) in DCM (2 mL) was added oxalyl chloride (2.00 equiv., 170 μL) and DMF (two drops) and the mixture stirred at rt for 1 h. The solvent and excess oxalyl chloride were then removed *in vacuo* and a solution of diamine **538** (188 mg, 0.710 mmol) in DCM (5 mL) was added, followed by pyridine (1.20 equiv., 97 μL) and DMAP (5 mg). The solution was stirred for 24 h. Water (20 mL) was then added and the mixture extracted with DCM (3x20 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude di-amide **540**. Purification by flash column chromatography (Petrol:Et_2O 4:1) gave di-amide **540** (111 mg, 32%) as a colourless oil; R_f 0.23 (Petrol:Et_2O 4:1); IR υ_{max} (thin film) 3352 br (N-H), 2958 m

(C-H), 1714 m (C=O), 1684 m (C=O), 1649 s (C=O), 1510 s, 1467 m, 1368 m, 1297 m, 1251 m, 1171 m, 1147 m, 1074 m, 1035 m, 831 m cm^{-1}; ^{1}H NMR (600 MHz) δ 0.71 (3H, d, *J* = 6.6, C*H*$_3$), 0.72 (3H, d, *J* = 6.7, C*H*$_3$), 0.90-1.00 (18H, m, C*H*$_3$), 1.05 (2H, m, CHC*H*$_2$CH), 1.73 (1H, m, C*H*(CH$_3$)$_2$), 1.97 (1H, m, C*H*(CH$_3$)$_2$), 2.12 (2H, m, C*H*(CH$_3$)$_2$), 2.33 (2H, m, C*H*$_2$), 2.72 (2H, m, C*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 3.87 (1H, m, C*H*NH), 4.83 (1H, br. s, C*H*NAr), 6.77 (1H, br. d, *J* = 10.9, N*H*CO), 6.83 (2H, app. d, *J* = 8.7, C*H*$_{PMPC3-H}$), 7.03 (2H, app. d, *J* = 8.7, C*H*$_{PMPC2-H}$); ^{13}C NMR (150 MHz) δ 16.7 (*C*H$_3$), 20.2 (*C*H$_3$), 21.8 (*C*H$_3$), 22.1 (*C*H$_3$), 22.4 (*C*H$_3$), 22.5 (*C*H$_3$), 23.2 (*C*H$_3$), 23.6 (*C*H$_3$), 24.5 (*C*H), 24.8 (*C*H), 29.2 (CH$_2$*C*HNAr), 36.4 (CH*C*H$_2$CH), 45.2 (*C*H$_2$CO), 49.1 (*C*H$_2$CO), 55.4 (O*C*H$_3$), 55.8 (*C*HNHCO), 114.5 (*C*H Arom.), 127.3 (*C*q Arom.), 131.1 (*C*H Arom.), 159.8 (ArN*C*=O), 160.2 (*C*q Arom.), 169.3 (NH*C*=O), 198.6 (CH$_2$*C*=O), 200.2 (CH$_2$*C*=O); *m/z* (CI^+) 489 ($M+H^+$, 60%), 471 ($M+H^+$-H_2O, 61%), 359 (40%), 93 (100%); HRMS: found 489.33410, $C_{28}H_{45}N_2O_5$ requires 489.33230.

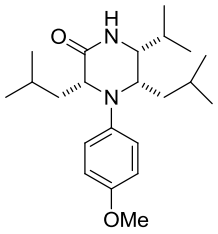
(5*S,6*R**,*Z*)-5-Isobutyl-6-isopropyl-4-(4-methoxyphenyl)-3-(2-methylpropylidene)piperazin-2-one 541**[234]



To a solution of diamine **538** (61 mg, 0.23 mmol) in THF (5 mL) was added at rt *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC, 67 mg, 0.35 mmol) and 1-hydroxybenzotriazole hydrate (47 mg, 0.35 mmol) followed by a solution of ketoacid **519** (30 mg, 0.23 mmol) in DCM (5 mL). The mixture was stirred at rt for 24 h, then diluted with DCM (20 mL) and washed with brine (10 mL). The combined organics were then dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:EtOAc 7:3) gave piperazinone **541** (57 mg, 69%) as a brown solid; mp. 152-153 ^{o}C; R_f 0.30 (Petrol:EtOAc 7:3); IR υ_{max} (thin film) 3209 br (N-H), 2956 w (C-H), 1671 s (C=C), 1622 s, 1499 s, 1464 m, 1442 m, 1409 m, 1384 m, 1366 m, 1331 m, 1283 m, 1241 s, 1180 m, 1153 m, 1037 m, 826 s, 767 m cm^{-1}; ^{1}H NMR (600 MHz) δ 0.68 (3H, d, *J* = 6.6, C*H*$_3$), 0.79 (3H, d, *J* = 6.6,

CH_3), 0.88 (3H, d, J = 6.6, CH_3), 0.93 (3H, d, J = 6.5, CH_3), 0.95 (3H, d, J = 6.7, CH_3), 1.07 (3H, d, J = 6.5, CH_3), 1.07 (1H, m, CH_2), 1.55 (1H, m, CH_2), 1.55 (1H, m, CH(CH_3)$_2$), 1.94 (1H, m, CH(CH_3)$_2$), 2.43 (1H, m, CH(CH_3)$_2$), 3.18 (1H, dd, J = 10.3, 3.6, CHNH), 3.53 (1H, br. d, J = 12.2, NCHCH_2), 3.76 (3H, s, OCH_3), 5.89 (1H, br. S, NH), 6.48 (1H, d, J = 10.6, =CH), 6.78 (2H, app. d, J = 8.8, CH Arom.), 6.89 (2H, app. d, J = 8.8, CH Arom.); ^{13}C NMR (150 MHz) δ 17.9 (*C*H$_3$), 19.4 (*C*H$_3$), 20.3 (*C*H$_3$), 21.5 (*C*H$_3$), 22.2 (*C*H$_3$), 23.7 (*C*H$_3$), 24.1 (*C*H(CH$_3$)$_2$), 26.4 (*C*H(CH$_3$)$_2$), 29.0 (*C*H(CH$_3$)$_2$), 34.4 (*C*H$_2$), 55.4 (O*C*H$_3$), 58.0 (*C*HNH), 58.8 (N*C*HCH$_2$), 114.3 (*C*H Arom.), 122.0 (*C*H Arom.), 129.7 (=*C*q), 140.0 (=*C*H), 143.4 (*C*q Arom.), 154.3 (*C*q Arom.), 164.3 (*C*=O); *m/z* (EI$^+$) 306 (M$^+$, 100%), 263 (M+H$^+$-CS, 95%), 249 (61%); HRMS: found 306.17595, $C_{22}H_{35}N_2O_2$ requires 306.17604.

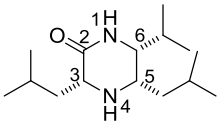
(3*R,5*S**,6*R**)-3,5-diisobutyl-6-isopropyl-4-(4-methoxyphenyl)piperazin-2-one 542**



To a solution of piperazinone **541** (170 mg, 0.470 mmol) in MeOH (10 mL) was added at rt palladium on carbon (50 mg, 10% by weight, 0.047 mmol) and the mixture was flushed with hydrogen, then stirred under a hydrogen atmosphere (balloon). After the piperazinone starting material was consumed (TLC, 4 h) the mixture was filtered through celite® and washed with DCM (20 mL) and evaporated *in vacuo* to give crude piperazinone **542**. Purification by flash column chromatography (Petrol:Me$_2$CO 4:1) gave the product (170 mg, 100%) as a colourless oil; Rf 0.50 (Petrol:Me$_2$CO 4:1); IR υ_{max} (thin film) 3207 br (N-H), 2954 m (C-H), 1658 s (C=O), 1505 (C=C), 1465 m, 1367 m, 1242 s, 1180 m, 1039 m, 827 m, 788 m, 733 m cm^{-1}; ^{1}H NMR (600 MHz) δ 0.70 (3H, d, J = 6.5, CH_3), 0.77 (3H, d, J = 6.7, CH_3), 0.90 (3H, d, J = 6.7, CH_3), 0.97 (3H, d, J = 6.5, CH_3), 0.98 (3H, d, J = 6.8, CH_3), 1.03 (3H, d, J = 6.5, CH_3), 1.03 (1H, m, CHCHCH_2), 1.55 (1H, m, CHCHCH_2), 1.55 (1H, m, O=CCHCH_2), 1.55 (1H, m, CHCH(CH$_3$)$_2$), 1.84 (1H, m, O=CCHCH_2), 1.92 (1H, m, O=CCHCH$_2$CH(CH$_3$)$_2$), 2.06 (1H, m, CHCHCH$_2$CH(CH$_3$)$_2$), 3.18 (1H, dd, J = 10.0, 3.5, NHCH), 3.37 (1H,

dt, *J* = 12.4, 3.1, NHCHC*H*N), 3.77 (3H, s, OCH_3), 4.09 (1H, dd, *J* = 9.9, 4.5, O=CC*H*), 6.02 (1H, br. S, N*H*), 6.80 (2H, app. d, *J* = 8.9, C*H* Arom.), 6.91 (2H, app. d, *J* = 8.9, C*H* Arom.); ^{13}C NMR (150 MHz) δ 18.0 (*C*H_3), 19.5 (*C*H_3), 21.5 (*C*H_3), 21.6 (*C*H_3), 23.3 (*C*H_3), 23.4 (CHCHCH$_2$*C*H(CH$_3$)$_2$), 23.7 (*C*H_3), 24.7 (O=CCHCH$_2$*C*H(CH$_3$)$_2$), 29.2 (NHCH*C*H(CH$_3$)$_2$), 34.7 (*C*H$_2$CHCH), 44.0 (*C*H$_2$CHC=O), 55.4 (O*C*H$_3$), 57.2 (N*C*HC=O), 58.4 (N*C*HCH), 58.5 (NH*C*H), 114.5 (*C*H Arom.), 122.6 (*C*H Arom.), 146.2 (*C*q Arom.), 154.3 (*C*q Arom.), 173.9 (*C*=O); *m/z* (EI$^+$) 360 (M$^+$, 15%), 303 (18%), 192 (100%); HRMS: found 360.27742, $C_{22}H_{36}N_2O_2$ requires 360.27713.

(3*R,5*S**,6*R**)-3,5-diisobutyl-6-isopropylpiperazin-2-one 511**[116]



To a solution of piperazinone **542** (320 mg, 0.880 mmol) in MeCN (10 mL) cooled to 0 ^{o}C was added a solution of CAN (2.08 g, 3.52 mmol) in H_2O (10 mL) dropwise over 3 min. The solution turned from pale yellow to dark orange. The mixture was stirred at this temperature for a further 2 h, over which the solution became light orange. Water (30 mL) was then added and the mixture extracted with EtOAc (3x20 mL), washed with saturated aqueous $NaHCO_3$ (40 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give crude pyrrolidinone **511**. Purification by flash column chromatography (Petrol:Me$_2$CO 3:2) gave pyrrolidinone **511** (91 mg, 41%) as a brown oil; R_f 0.53 (Petrol:Me$_2$CO 3:2); IR υ_{max} (thin film) 3209 w (N-H), 2955 (C-H), 1658 s (C=O), 1467 m, 1367 m, 1165 w, 918 w, 722 w cm^{-1}; ^{1}H NMR (600 MHz) δ 0.87-0.99 (18H, m, C*H*$_3$), 1.30 (2H, m, C*H*$_2$C^{3}H), 1.40 (1H, m, C^{3}HC*H*$_2$), 1.65 (1H, m, C^{5}HC*H*$_2$C*H*(CH$_3$)$_2$), 1.74 (1H, m, C^{3}HCH$_2$C*H*(CH$_3$)$_2$), 1.90 (1H, m, C^6*H*(CH$_3$)$_2$), 1.90 (1H, m, C^{3}HC*H*$_2$), 3.07 (1H, m, C^6*H*), 3.15 (1H, ddd, *J* = 8.5, 5.8, 4.3, C^5*H*), 3.40 (1H, dd, *J* = 10.2, 3.4, C^3*H*), 6.22 (1H, br. s, N^1*H*), N^4*H* peak missing; ^{13}C NMR (125 MHz) δ 17.1 (*C*H_3), 20.0 (*C*H_3), 21.6 (*C*H_3), 22.4 (*C*H_3), 23.1 (*C*H_3), 23.7 (*C*H_3), 24.4 (C*H*), 24.8 (C*H*), 27.9 (C^{6}HC*H*), 40.5 (C^{5}HCH$_2$), 41.1 (C^{3}HCH$_2$), 53.3 (*C*^{5}H), 56.9 (*C*^{3}H), 59.4 (*C*^{6}H),174.3 (*C*^{2}=O); *m/z* (EI$^+$) 254 (M$^+$, 30%), 197 (22%), 169 (43%), 154 (31%); HRMS found 254.23550, $C_{15}H_{30}N_2O$ requires 254.23527.

4. Appendixes

4.1 Appendix 1 – Table of coupling constants for pyrrolidinones 232

The coupling constants of all the pyrrolidinones synthesised during our study are presented in the following table. Coupling J_{HaHb} refers to the coupling constant between protons H_a and H_b (Figure 41) and J_{HbHc} between protons H_b and H_c. The notation J_{HaHb} refers to the coupling seen in the signal of proton H_a and J_{HbHa} to that of proton H_b. The constants presented are not averaged.

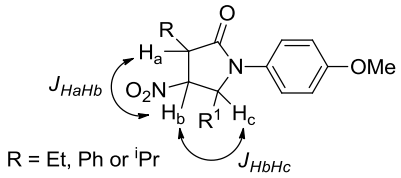
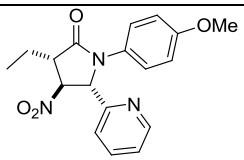
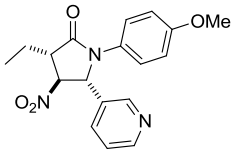
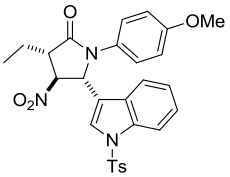
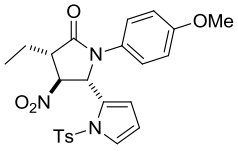
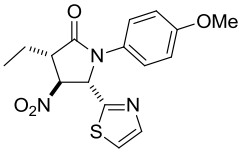
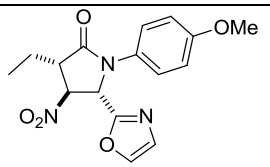
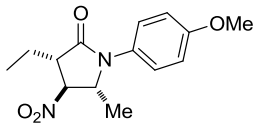
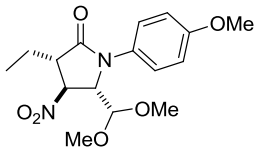
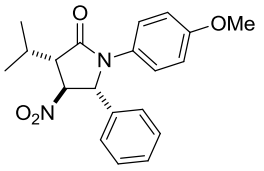
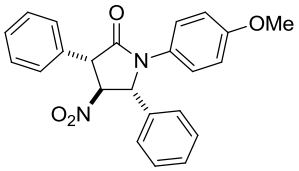
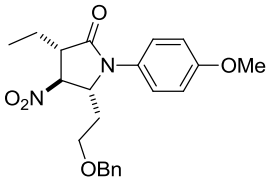
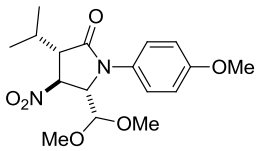
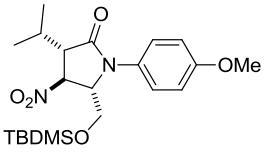
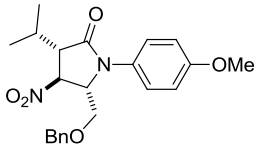
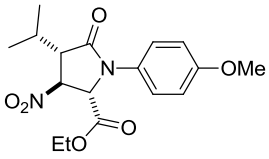


Figure 41

Table 23. Coupling constants of synthesised pyrrolidinones.

Entry	Structure	J_{HaHb}	J_{HbHa}	J_{HbHc}	J_{HcHb}
1		5.8	5.8	4.4	4.4
2		7.3	7.2	5.7	5.9
3		6.7	6.7	5.2	5.3
4		4.7	-[a]	-[a]	-[a]
5		5.0	5.1	3.8	4.2

6		5.7	5.6	4.4	4.4
7		7.3	7.2	5.7	6.2
8		4.6	4.9	3.4	3.2
9		7.6	7.6	5.9	5.9
10		8.0	8.0	6.3	6.2
11		-[a]	6.0	4.6	4.6
12		6.7	6.6	4.8	4.7
13		7.9	7.9	6.0	-[a]
14		7.0	7.1	5.3	-[a]
15		4.9	4.9	3.7	3.7

[a]Could not be distinguished.

4.2 Appendix 2 – Table of coupling constants for *β*-nitroamines 379 and trifluoroacetamides 452

The values of coupling constants of all the crude *β*-nitroamines **379** from the nitro-Mannich reaction of *β*-nitrostyrene adducts and the trifluoroacetamides **452** derived after protection with TFAA and pyridine are presented in the following table. Coupling J_{HaHb} refers to the coupling constant between protons H_a and H_b (Figure 42) and J_{HbHc} between protons H_b and H_c. The notation J_{HaHb} refers to the coupling seen in the signal of proton H_a and J_{HbHa} to that of proton H_b. The constants presented are not averaged.

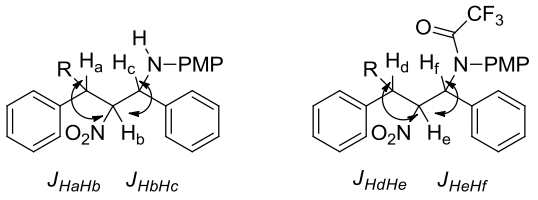


Figure 42: Protons referring to coupling constants in the ^{1}H NMR spectra.

Table 24. Coupling constants for C-substituted crude *β*-nitroamines.

R group	J_{HaHb}	J_{HbHa}	J_{HbHc}	J_{HcHb}	*dr*
3-indoline	11.5	11.5	3.4	-[a]	95:5
1,3,5-trimethoxybenzyl	12.2	-[a]	-[a]	-[a]	>95:5

Table 25. Coupling constants for C-substituted trifluoroacetamides.

R group	J_{HdHe}	J_{HeHd}	J_{HeHf}	J_{HfHe}	Stereochemistry
3-indoline	2.8	-[a]	-[a]	-[a]	*anti, anti*
1,3,5-trimethoxybenzyl	11.5	11.5	6.8	6.8	*anti, anti*

Table 26. Coupling constants for alkoxy-substituted crude *β*-nitroamines.

Entry	R group	J_{HaHb}	J_{HbHa}	J_{HbHc}	J_{HcHb}	*dr*
1	MeO-	9.2	9.2	5.3	5.4	90:10
2	EtO-	9.2	9.3	5.8	5.8	>95:5
3	BnO-	9.1	9.2	5.3	5.3	90:10
4	^{i}PrO-	8.8	8.8	6.2	6.0	>95:5

Table 27. Coupling constants for alkoxy-substituted trifluoroacetamides.

Entry	R group	J_{HdHe}	J_{HeHd}	J_{HeHf}	J_{HfHe}	Stereochemistry
1	MeO-	8.4	8.5	10.9	11.0	*anti, anti*
2	EtO-	8.4	8.5	10.9	10.9	*anti, anti*
3	BnO-	6.7	6.8	11.0	11.0	*anti, anti*
4	^{i}PrO-	7.7	7.7	10.7	10.8	*anti, anti*

Table 28. Coupling constants for N-substituted crude *β*-nitroamines.

Entry	R group	J_{HaHb}	J_{HbHa}	J_{HbHc}	J_{HcHb}	*dr*
1	*p*-$NO_2C_6H_4NH$-	-[a]	9.1	6.2	6.3	90:10
2	1*H*-benzotriazol-1-yl	-[a]	-[a]	-[a]	-[a]	>95:5
3	Oxazolidin-2-one	-[a]	-[a]	-[a]	-[a]	75:25

Table 29. Coupling constants for N-substituted trifluoroacetamides.

Entry	R group	J_{HdHe}	J_{HeHd}	J_{HeHf}	J_{HfHe}	Stereochemistry
1	*p*-$NO_2C_6H_4NH$-	3.1	3.1	10.8	10.8	*anti, anti*
2	1*H*-benzotriazol-1-yl	10.7	-[a]	-[a]	6.3	*anti, anti*
3	Oxazolidin-2-one	10.3	9.9	7.9	7.8	*anti, anti*

Table 30. Coupling constants for S-substituted crude *β*-nitroamines.

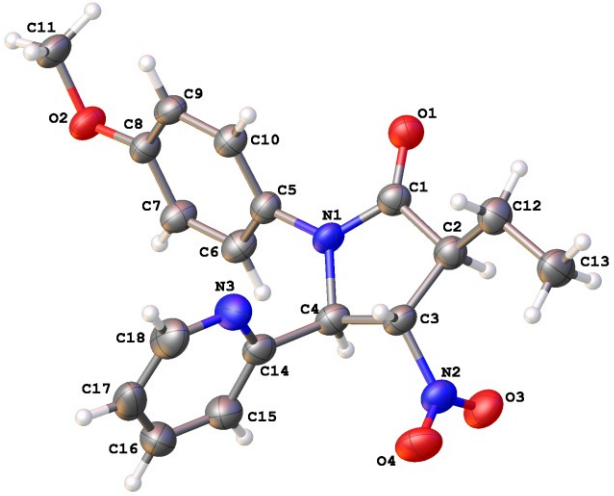
R group	J_{HaHb}	J_{HbHa}	J_{HbHc}	J_{HcHb}	*dr*
^{n}BuS-	11.0	11.0	3.5	-[a]	60:40
PhS-	9.5	9.4	5.3	-[a]	65:35

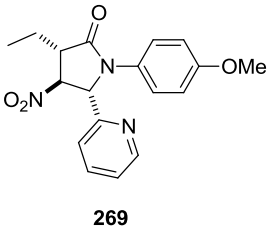
Table 31. Coupling constants for S-substituted trifluoroacetamides.

R group	J_{HdHe}	J_{HeHd}	J_{HeHf}	J_{HfHe}	Stereochemistry
^{n}BuS-	6.2	6.2	10.4	10.3	*anti, anti*
PhS-	5.1	5.1	9.8	9.8	*anti, anti*

4.3 Appendix 3 – Crystallography data

(3*S, 4*S**, 5*S**)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-(pyridin-2-yl)pyrrolidin-2-one 269**





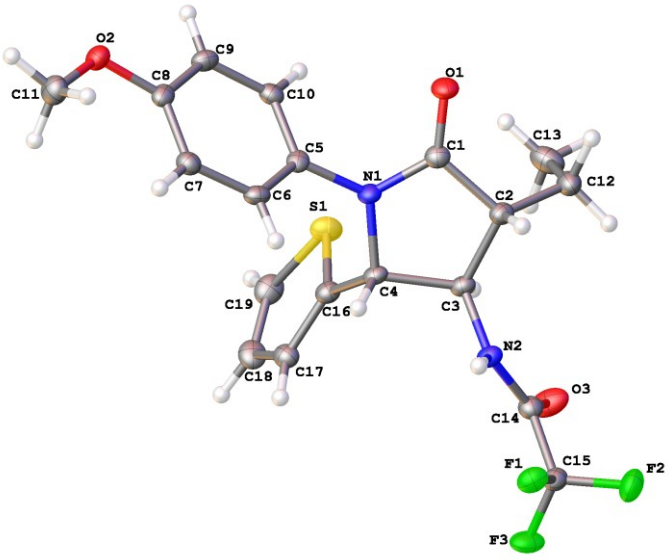
269

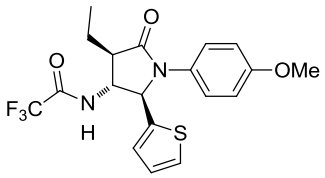
Table 32. Crystal data and structure refinement at 100(2) K.

Empirical formula	$C_{18}H_{19}N_3O_4$	
Formula weight	341.36	
Wavelength	1.54187 Å	
Crystal system	Monoclinic	
Space group	*P*21/*c*	
Unit cell dimensions	a = 12.6533(8) Å	α = 90°
	b = 15.8418(2) Å	β = 105.971(8)°
	c = 8.85870(10) Å	γ = 90°
Volume	1707.19(11) $Å^3$	
Z	4	
Density (calculated)	1.328 Mg / m^3	
Absorption coefficient	0.789 mm^{-1}	
F(000)	720	
Crystal	Plate; Colourless	
Crystal size	0.07 × 0.01 × 0.01 mm^3	
θ range for data collection	6.67 – 66.44°	
Index ranges	$-11 \le h \le 15$, $-18 \le k \le 18$, $-10 \le l \le 10$	
Reflections collected	11691	

Independent reflections	2947 [R_{int} = 0.0855]
Completeness to θ = 66.44°	98.1 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9922 and 0.9469
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2947 / 0 / 229
Goodness-of-fit on F^2	1.062
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0739, $wR2$ = 0.2028
R indices (all data)	$R1$ = 0.0900, $wR2$ = 0.2354
Extinction coefficient	0.0068(15)
Largest diff. peak and hole	0.362 and –0.337 e Å^{-3}
Diffractometer type	Rigaku Saturn724+ area detector (ω scans
to fill asymmetric unit sphere)	
Cell determination	CrystalClear-SM Expert 2.0 r7 (Rigaku
2011)	

N-((2*R*, 3*R*, 4*R*)-4-ethyl-1-(4-methoxyphenyl)-5-oxo-2-(thiophen-2-yl)pyrrolidin-3-yl)-2,2,2-trifluoroacetamide 287





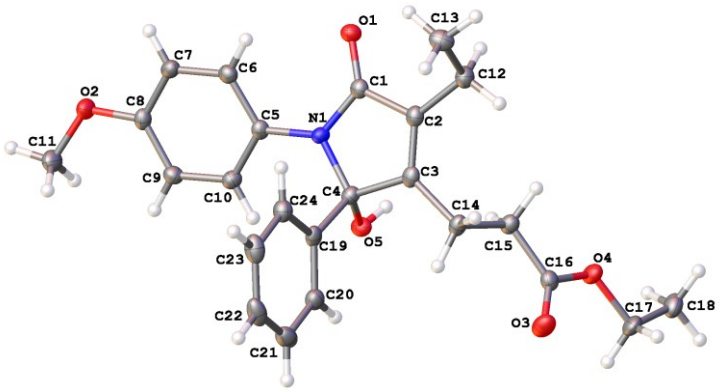
287

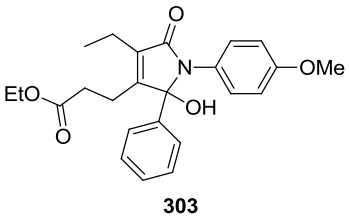
Table 33. Crystal data and structure refinement at 100(2) K.

Empirical formula	$C_{19}H_{19}F_3N_2O_3S$
Formula weight	412.42

Wavelength	1.54187 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 8.33990(10) Å	α = 90°
	b = 10.16140(10) Å	β = 90°
	c = 22.2832(15) Å	γ = 90°
Volume	1888.39(13) $Å^3$	
Z	4	
Density (calculated)	1.451 Mg / m^3	
Absorption coefficient	2.000 mm^{-1}	
F(000)	856	
Crystal	Cut Block; Colourless	
Crystal size	0.26 × 0.22 × 0.16 mm^3	
θ range for data collection	6.63 – 66.37°	
Index ranges	$-7 \le h \le 9$, $-12 \le k \le 10$, $-24 \le l \le 26$	
Reflections collected	7566	
Independent reflections	3114 [Rint = 0.0329]	
Completeness to θ = 66.37°	97.2 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.7402 and 0.6244	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3114 / 0 / 255	
Goodness-of-fit on F2	1.058	
Final R indices [$F^2 > 2\sigma(F^2)$]	R1 = 0.0248, wR2 = 0.0635	
R indices (all data)	R1 = 0.0253, wR2 = 0.0637	
Absolute structure parameter	0.011(13)	
Largest diff. peak and hole	0.161 and –0.173 e $Å^{-3}$	
Diffractometer type	Rigaku Saturn724+ area detector (ω scans	
to fill asymmetric unit sphere)		
Cell determination	CrystalClear-SM Expert 2.0 r7 (Rigaku	
2011)		

Ethyl 3-(4-ethyl-2-hydroxy-1-(4-methoxyphenyl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)propanoate 303





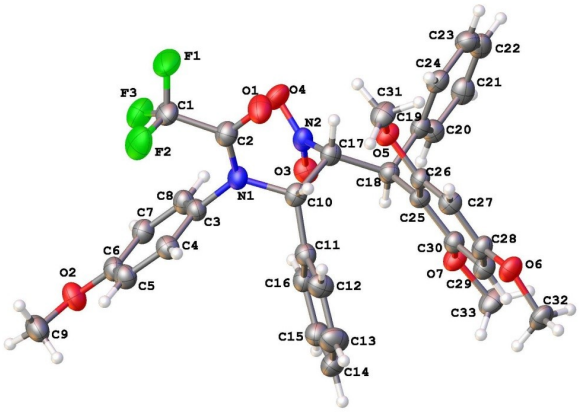
303

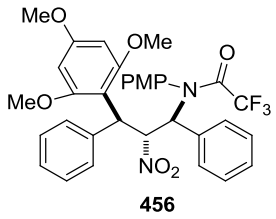
Table 34. Crystal data and structure refinement at 120(2) K.

Empirical formula	$C_{24}H_{27}NO_5$	
Formula weight	409.47	
Wavelength	0.71075 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 9.9597(6) Å	α = 66.695(5)°
	b = 10.7744(6) Å	β = 87.864(6)°
	c = 11.8214(8) Å	γ = 62.888(4)°
Volume	1021.04(11) $Å^3$	
Z	2	
Density (calculated)	1.332 Mg / m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	436	
Crystal	Prism; Colourless	
Crystal size	0.20 × 0.20 × 0.20 mm^3	
θ range for data collection	3.26 – 27.46°	
Index ranges	$-12 \le h \le 12$, $-13 \le k \le 13$, $-15 \le l \le 15$	
Reflections collected	10380	
Independent reflections	4598 [R_{int} = 0.0234]	
Completeness to θ = 27.46°	98.5 %	
Absorption correction	Semi–empirical from equivalents	

Max. and min. transmission	0.9816 and 0.9816
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4598 / 0 / 275
Goodness-of-fit on F^2	1.107
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0350, *wR2* = 0.0834
R indices (all data)	*R1* = 0.0551, *wR2* = 0.1051
Largest diff. peak and hole	0.364 and –0.239 e Å^{-3}
Diffractometer type	Rigaku Saturn724+ area detector (ω scans to fill asymmetric unit sphere)
Cell determination	CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R,2*S**,3*R**)-2-nitro-1,3-diphenyl-3-(2,4,6-trimethoxyphenyl)propyl)acetamide 456**





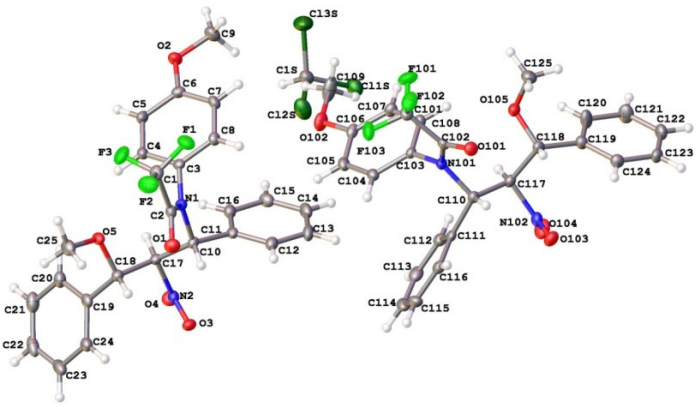
456

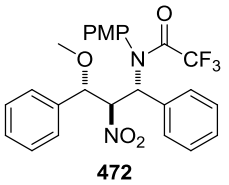
Table 35. Crystal data and structure refinement at 120(2) K.

Empirical formula	$C_{33}H_{31}F_3N_2O_7$	
Formula weight	624.60	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 11.9846(6) Å	α = 63.816(5)°
	b = 12.2669(4) Å	β = 64.578(5)°
	c = 12.7033(8) Å	γ = 80.069(6)°
Volume	1513.31(13) Å^3	

Z	2
Density (calculated)	1.371 Mg / m^3
Absorption coefficient	0.108 mm^{-1}
F(000)	652
Crystal	Prism; Colourless
Crystal size	0.25 × 0.21 × 0.10 mm^3
θ range for data collection	3.19 – 25.03°
Index ranges	$-14 \le h \le 14$, $-13 \le k \le 14$, $-15 \le l \le 15$
Reflections collected	17291
Independent reflections	5343 [R_{int} = 0.0320]
Completeness to θ = 25.03°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9892 and 0.9734
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5343 / 0 / 411
Goodness-of-fit on F^2	1.085
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0606, *wR2* = 0.1772
R indices (all data)	*R1* = 0.0933, *wR2* = 0.2630
Extinction coefficient	0.042(8)
Largest diff. peak and hole	0.453 and –0.435 e Å^{-3}
Diffractometer type	*Rigaku R-Axis Spider* including curved Fujifilm image plate and a graphite monochromated sealed tube Mo generator.
Cell determination	CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)

2,2,2-Trifluoro-*N*-((1*R,2*R**,3*S**)-3-methoxy-2-nitro-1,3-diphenylpropyl)-*N*-(4-methoxyphenyl)acetamide 472**





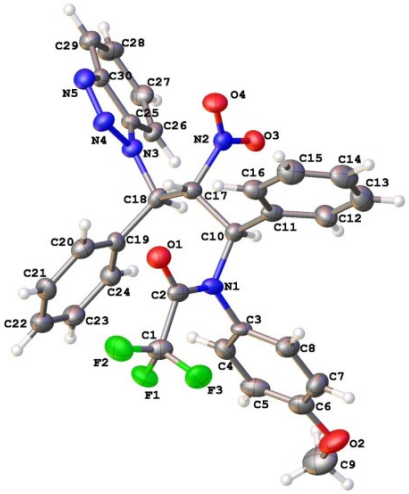
472

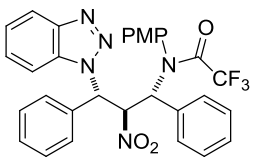
Table 36. Crystal data and structure refinement at 100(2) K.

Empirical formula	$C_{25.50}H_{23.50}Cl_{1.50}F_3N_2O_5$	
Formula weight	548.14	
Wavelength	0.71075 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 11.7772(3) Å	α = 69.247(5)°
	b = 14.4495(4) Å	β = 77.347(6)°
	c = 17.3239(12) Å	γ = 66.473(5)°
Volume	2517.3(2) Å^3	
Z	4	
Density (calculated)	1.446 Mg / m^3	
Absorption coefficient	0.267 mm^{-1}	
F(000)	1132	
Crystal	Block; Colourless	
Crystal size	0.07 × 0.05 × 0.03 mm^3	
θ range for data collection	3.02 – 27.48°	
Index ranges	$-12 \le h \le 15$, $-17 \le k \le 18$, $-22 \le l \le 22$	
Reflections collected	34108	
Independent reflections	11500 [R_{int} = 0.0491]	
Completeness to θ = 27.48°	99.5 %	
Absorption correction	Semi–empirical from equivalents	

Max. and min. transmission	0.9920 and 0.9815
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11500 / 0 / 671
Goodness-of-fit on F^2	1.068
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0442, *wR2* = 0.0992
R indices (all data)	*R1* = 0.0712, *wR2* = 0.1120
Largest diff. peak and hole	0.359 and –0.607 e Å^{-3}
Diffractometer type	Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100µm focus)
Cell determination	CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)

_N_-((1_R_*,2_R_*,3_S_*)-3-(1_H_-benzo[_d_][1,2,3]triazol-1-yl)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide 482





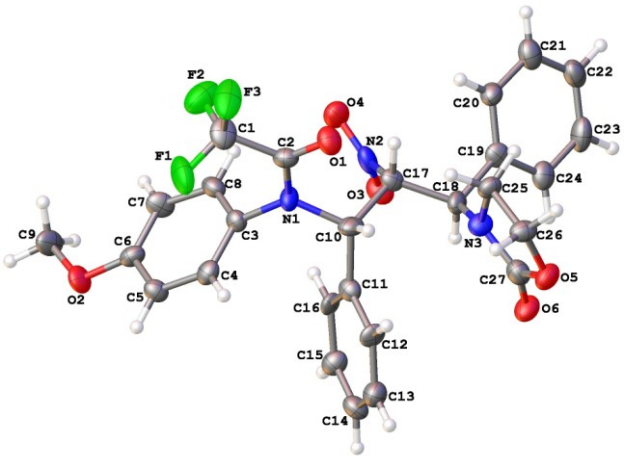
482

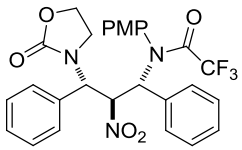
Table 37. Crystal data and structure refinement at 100(2) K.

Empirical formula	$C_{30}H_{24}F_3N_5O_4$
Formula weight	575.54
Wavelength	0.71075 Å
Crystal system	Monoclinic
Space group	*P*21/*c*
Unit cell dimensions	a = 16.6181(15) Å α = 90°

	b = 14.1560(13) Å β = 93.776(7)°
	c = 11.7132(10) Å γ = 90°
Volume	2749.5(4) Å^3
Z	4
Density (calculated)	1.390 Mg / m^3
Absorption coefficient	0.108 mm^{-1}
F(000)	1192
Crystal	Platelet; Colourless
Crystal size	0.04 × 0.04 × 0.01 mm^3
θ range for data collection	3.13 – 25.03°
Index ranges	$-19 \le h \le 18$, $-16 \le k \le 16$, $-13 \le l \le 12$
Reflections collected	15500
Independent reflections	4823 [R_{int} = 0.1439]
Completeness to θ = 25.03°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9989 and 0.9957
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4823 / 0 / 380
Goodness-of-fit on F^2	0.989
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0820, *wR2* = 0.1534
R indices (all data)	*R1* = 0.1994, *wR2* = 0.1961
Largest diff. peak and hole	0.300 and –0.258 e Å^{-3}
Diffractometer type	Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100μm focus)
Cell determination	CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)

2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-(2-nitro-3-(2-oxooxazolidin-3-yl)-1,3-diphenylpropyl)acetamide 480





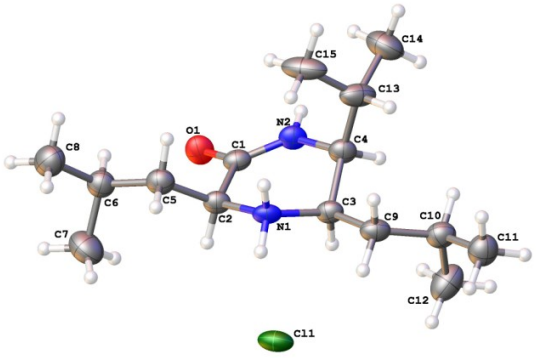
480

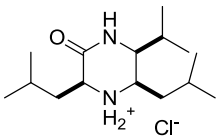
Table 38. Crystal data and structure refinement at 100(2) K.

Empirical formula	$C_{27}H_{24}F_3N_3O_6$	
Formula weight	543.49	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	*P*21/*n*	
Unit cell dimensions	a = 9.1677(14) Å	α = 90°
	b = 9.7544(14) Å	β = 97.894(7)°
	c = 28.121(5) Å	γ = 90°
Volume	2490.9(7) Å^3	
Z	4	
Density (calculated)	1.449 Mg / m^3	
Absorption coefficient	0.118 mm^{-1}	
F(000)	1128	
Crystal	Plate; Colourless	
Crystal size	0.03 × 0.03 × 0.01 mm^3	
θ range for data collection	3.03 – 25.03°	
Index ranges	$-10 \le h \le 10$, $-11 \le k \le 10$, $-25 \le l \le 33$	
Reflections collected	11836	
Independent reflections	4246 [R_{int} = 0.2162]	
Completeness to θ = 25.03°	96.6 %	

Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9988 and 0.9965
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4246 / 0 / 354
Goodness-of-fit on F^2	0.967
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0991, $wR2$ = 0.1774
R indices (all data)	$R1$ = 0.2528, $wR2$ = 0.2418
Extinction coefficient	0.0055(18)
Largest diff. peak and hole	0.342 and –0.341 e Å^{-3}
Diffractometer type	Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100µm focus)
Cell determination	CrystalClear-SM Expert 2.0 r7 (Rigaku 2011)

(2*S,3*R**,6*R**)-2,6-diisobutyl-3-isopropyl-5-oxopiperazin-1-ium chloride 548**





548

Table 39. Crystal data and structure refinement at 100(2) K.

Empirical formula	$C_{15}H_{31}ClN_2O$
Formula weight	290.87
Temperature	100(2) K
Wavelength	0.71075 Å
Crystal system	Monoclinic
Space group	*P*21/*c*
Unit cell dimensions	a = 12.6231(15) Å α = 90°

	b = 6.4267(7) Å	β = 92.323(7)°
	c = 23.920(3) Å	γ = 90°
Volume	1938.9(4) Å^3	
Z	4	
Density (calculated)	0.996 Mg / m^3	
Absorption coefficient	0.194 mm^{-1}	
F(000)	640	
Crystal	Blade; Colourless	
Crystal size	0.22 × 0.03 × 0.01 mm^3	
θ range for data collection	3.23 – 27.48°	
Index ranges	$-16 \le h \le 16$, $0 \le k \le 8$, $0 \le l \le 30$	
Reflections collected	4443	
Independent reflections	4443 [R_{int} = 0.0000]	
Completeness to θ = 27.48°	99.9 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9981 and 0.9585	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4443 / 0 / 178	
Goodness-of-fit on F^2	1.045	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0726, *wR2* = 0.1803	
R indices (all data)	*R1* = 0.1159, *wR2* = 0.1966	
Largest diff. peak and hole	0.416 and –0.249 e Å^{-3}	
Diffractometer type	Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100µm focus)	
Cell determination	CrystalClear-SM Expert 2.0 r11 (Rigaku 2011)	

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